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(71) Applicants (for all designated States except US): COLEY PHARMACEUTICAL GmbH [DE/DE]; Elisabeth-Selbert-Strasse 9, D-40764 Langenfeld (DE). COLEY PHARMACEUTICAL GROUP, INC. [US/US]; 93 Worcester Street, Suite 101, Wellesley, MA 02481 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): VOLLMER, Jörg [DE/DE]; Kohlranschweg 24, D-40591 Duesseldorf (DE).

JURK, Marion [DE/DE]; Klosterstr. 4, D-41540 Dornagel (DE). LIPFORD, Grayson, B. [GB/US]; 38 Bates Road, Watertown, MA 02472 (US). SCHETTER, Christian [DE/DE]; Oerkhaushof 35, D-40723 Hilden (DE). FORSBACH, Alexandra [DE/DE]; Raiffeisenstrasse N°1, D-40764 Rantingen (DE). KRIEG, Arthur, M. [US/US]; 173 Winding River Road, Wellesley, MA 02482 (US).

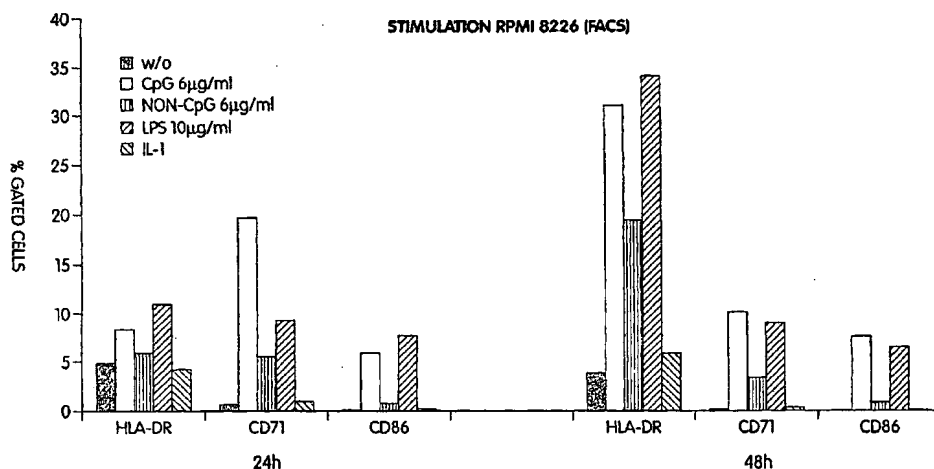
(74) Agent: TREVISAN, Maria, A.; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210 (US).

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(54) Title: METHODS AND PRODUCTS FOR IDENTIFICATION AND ASSESSMENT OF TLR LIGANDS



(57) Abstract: The invention provides in part novel screening methods and compositions for identifying and distinguishing between candidate immunomodulatory compounds. The invention further provides methods for assessing biological activity of composition containing a known TLR ligand. These latter methods can be used for quality assessment and selection of various lots of test compositions, including pharmaceutical products for clinical use.

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**METHODS AND PRODUCTS FOR IDENTIFICATION AND ASSESSMENT**  
**OF TLR LIGANDS**

**Background of the Invention**

5       Nucleic acids with immunostimulatory activity have been identified. The first recognized immunostimulatory motif was the CpG motif in which at least the C of the dinucleotide was unmethylated. It has been postulated that mammalian subjects recognize the unmethylated dinucleotide as being of bacterial origin, and thus mount a heightened immune response following exposure. The ensuing immune response includes both cell mediated and  
10       humoral aspects. Since the discovery of the CpG immunostimulatory motif, other immunostimulatory motifs have also been identified including the poly-T and T-rich motifs, the TG motif and the poly-G motif. In some instances, immunostimulation has also been observed in response to exposure to methylated CpG motifs and motif-less nucleic acids having phosphorothioate backbone linkages.

15       The responses induced by immunostimulatory nucleic acids are varied and can include production and secretion of cytokines, chemokines, and other growth factors. The nucleic acids can induce a heightened immune stimulation regardless of whether an antigen is also introduced to the subject. Identification of new motifs as well as of subtle differences between response profiles of different nucleic acids oftentimes can be laborious, and a high  
20       throughput system for screening nucleic acids for their ability to be immunostimulatory as well as to determine the profile of responses they induce would be useful.

**Summary of the Invention**

25       The invention provides in its broadest sense screening methods and tools for identification and discrimination of immunomodulatory molecules and assessment and standardization of samples containing known immunomodulatory molecules. The immunomodulatory molecules can be immunostimulatory or immunoinhibitory, and most preferably are Toll-like receptor (TLR) ligands.

30       In one aspect, the invention provides a screening method for identifying TLR agonists. The method comprises contacting a cell line endogenously expressing at least one TLR with a test compound and measuring a test level of TLR signaling activity, wherein a positive test level is indicative of a TLR agonist (i.e., an immunostimulatory compound). The positive test

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level may be apparent without referring to a control. Preferably, however, it is determined relative to a control (i.e., the TLR signaling activity from a reference compound).

In some embodiments, the reference compound is a compound that induces no response (i.e., a zero response) or a minimal response. In this case, a test level that is greater  
5 than the reference level is indicative of a compound with TLR signaling activity. More preferably, the reference compound is a compound that induces a positive response (i.e., a non-zero response) and that is immunostimulatory. These reference compounds are referred to herein as negative and positive reference compounds, respectively. If the reference compound is immunostimulatory (i.e., a positive reference compound), a non-zero test level  
10 that is lower than the reference level is still indicative of an immunostimulatory test compound. In this latter embodiment, the test compound is less immunostimulatory than the reference compound (for that particular readout), but it is nonetheless immunostimulatory given the non-zero response induced. There may be one or more concurrent or consecutive assays with a negative reference compound, a positive reference compound, or both. The  
15 reference may also be a standard curve or data generated previously.

In a related aspect, the screening method involves exposing the same cell to a positive reference compound and a test compound in order to identify a test compound that inhibits the immunostimulatory response of the positive reference compound (i.e., a TLR antagonist or an immunoinhibitory compound).

20 In still a related aspect, the screening method involves exposing the same cells to a positive reference compound and a test compound in order to identify a test compound that enhances the immunostimulatory response of the positive reference compound (i.e., an enhancer).

In both of these latter aspects, the assay requires a co-incubation of the positive  
25 reference compound, the test compound and the cells. Separate assays with positive reference compound alone and optionally negative reference compound alone are usually also performed.

The positive reference compound is a known TLR ligand. Non-limiting examples include but are not limited to TLR3 ligands, TLR7 ligands, TLR8 ligands and TLR9 ligands.  
30 In some embodiments, the positive reference compound is an immunostimulatory nucleic acid. In some embodiments, the positive reference compound is a CpG nucleic acid, a poly-T nucleic acid, a T-rich nucleic acid or a poly-G nucleic acid. Another example of a positive



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reference compound is a nucleic acid comprising a backbone that contains at least one phosphorothioate linkage.

It has been further discovered according to the invention that the RPMI 8226 cell line expresses TLR7 and responds to the imidazoquinoline compound R-848 (Resiquimod) which is known to signal through TLR7 and TLR8. Accordingly, the screening method can be performed using RPMI 8226, Raji or RAMOS cells and an imidazoquinoline compound such as R-848 or R-847 (Imiquimod) as the positive reference compound.

In one embodiment, the test compound is a nucleic acid such as but not limited to a DNA, an RNA and a DNA/RNA hybrid. The test compound may be a nucleic acid that does not comprise motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a poly-G motif. The test compound may be a nucleic acid that comprises a phosphorothioate backbone linkage. In another embodiment, the test compound is a non-nucleic acid small molecule. The non-nucleic acid small molecule may be derived from a molecular library. In other embodiments, the test compound comprises amino acids, carbohydrates such as polysaccharides. It may be a hormone or a lipid or contain moieties derived therefrom. In other embodiments, the test compounds are putative ligands for TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10 or TLR11.

In one embodiment, the cell is a RPMI 8226 cell, a Raji cell, a RAMOS cell, a THP-1 cells, a Nalm cell or a KG-1 cell and the TLR is TLR9. In another embodiment, the cell is a RPMI 8226 cell, a Raji cell or a RAMOS cell and the TLR is TLR7. In yet another embodiment, the cell is a KG-1 cell, a Nalm cell, a Raji cell, a RAMOS cell, a Jurkat cell, a Hela cell, a Hep-2 cell, a Hep-2 cells, a A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell and the TLR is TLR3.

In another embodiment, the cell is an RPMI 8226 cell and the TLR is TLR7 or TLR9. In still another embodiment, the cell is a Raji cell and the TLR is TLR9, TLR7 or TLR3.

Depending upon the embodiment, the TLR signaling activity may be measured or detected in a number of ways. In one embodiment, the TLR signaling activity is measured by cytokine, chemokine, or growth factor secretion. The cytokine secretion may be selected from the group consisting of IL-6 secretion, IL-10 secretion, IL-12 secretion, IFN- $\alpha$  secretion and TNF- $\alpha$  secretion, but is not so limited. The chemokine secretion may be IP-10 secretion or IL-8 secretion, but is not so limited.

In another embodiment, the TLR signaling activity is measured by antibody secretion. The antibody secretion may be IgM secretion, but is not limited to this antibody subtype.

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In another embodiment, the TLR signaling activity is measured by phosphorylation. The total level of phosphorylation in the cell or the level of phosphorylation of particular factors in the cell may be measured. These factors are preferably signaling factors and can be selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, Jun, c-fos, and subunits of NF- $\kappa$ B, but are not so limited.

In still a further embodiment, the TLR signaling activity is measured by cell surface marker expression. In one embodiment, the TLR signaling activity is measured by an increase in cell surface marker expression. Examples of cell surface markers to be analyzed include CD71, CD86, HLA-DR, CD80, HLA Class I, CD54 and CD69. In other embodiments, the TLR signaling activity is measured by a decrease in cell surface marker expression. Cell surface marker expression can be determined using flow cytometry. TLR signaling activity can also be measured by protein production (e.g., by Western blot).

In another embodiment, the TLR signaling activity is measured by gene expression. Gene expression profiles may be determined using Northern blot analysis or RT-PCR that uses mRNA or total RNA as a starting material. The gene expression of interest may be that of the chemokines and cytokines and cell surface molecules recited above. Gene expression analysis can be performed using microarray techniques.

In yet another embodiment, the TLR signaling activity is measured by cell proliferation. Cell proliferation assays can be measured in a number of ways including but not limited to  $^3$ H-thymidine incorporation.

In one embodiment, the cell is an RPMI 8226 cell and TLR signaling is indicated by expression of a marker such as CD71, CD86 and/or HLA-DR or by expression, production or secretion of a factor such as IL-8, IL-10, IP-10 and/or TNF- $\alpha$ . Preferably, in this latter embodiment, the RPMI 8226 cell is unmodified. In another embodiment, the cell is a Raji cell and the TLR signaling is indicated by IL-6 or IFN- $\alpha$ 2 expression, production or secretion. In yet another embodiment, the cell is a RAMOS cell and the TLR signaling is indicated by CD80 cell surface expression.

TLR signaling activity can be measured via a native readout or an artificial readout or both. A native readout is one that does not rely on introduction of a reporter construct into the cell of interest.

The cell line may be used in a modified or unmodified form. In one embodiment, the cell line is transfected with a reporter construct. The transfection may be transient or stable. The reporter construct generally comprises a promoter, a coding sequence and a

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polyadenylation signal. The coding sequence may comprise a reporter sequence selected from the group consisting of an enzyme (e.g., luciferase, alkaline phosphatase,  $\beta$ -galactosidase, chloramphenicol acetyltransferase (CAT), secreted alkaline phosphatase, etc.), a bioluminescence marker (e.g., green fluorescent protein (GFP, U.S. Patent No. 5,491,084), etc.), a surface-expressed molecule (e.g., CD25), a secreted molecule (e.g., IL-8, IL-12 p40, TNF- $\alpha$ , etc.), and other detectable protein sequences known to those of skill in the art. Preferably, the coding sequence encodes a protein, the level or activity of which can be quantified, with preferably a wide linear range.

In some embodiments, the promoter is a promoter that is responsive to TLR signaling pathways (i.e., a "TLR responsive promoter"). In some embodiments, the promoter contains a binding site for a transcription factor activated upon CpG nucleic acid exposure, such as for example NF- $\kappa$ B. In other embodiments, the promoter contains a binding site for a transcription factor that is activated by a positive reference compound other than CpG nucleic acids. The transcription factor binding site may be selected from the group consisting of a NF- $\kappa$ B binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE, as well as others known to those of skill in the art.

In another embodiment, the promoter contains a functional promoter element from an IL-1 gene, an IL-6 gene, an IL-8 gene, an IL-10 gene, an IL-12 p40 gene, an IFN- $\alpha$ 1 gene, an IFN- $\alpha$ 4 gene, an IFN- $\beta$  gene, an IFN- $\gamma$  gene, a TNF- $\alpha$  gene, a TNF- $\beta$  gene, an IP-9 gene, an IP-10 gene, a RANTES gene, an ITAC gene, a MCP-1 gene, an IGFBP4 gene, a CD54 gene, a CD69 gene, a CD71 gene, a CD80 gene, a CD86 gene, a HLA-DR gene, and a HLA class I gene.

The TLR responsive promoter may be a TLR1 responsive promoter, a TLR2 responsive promoter, a TLR3 responsive promoter, a TLR4 responsive promoter, a TLR5 responsive promoter, a TLR6 responsive promoter, a TLR7 responsive promoter, a TLR8 responsive promoter, a TLR9 responsive promoter, a TLR10 responsive promoter or a TLR11 responsive promoter.

In these latter embodiments, the cell line may be transfected with a reporter construct having a promoter derived from a particular cytokine, chemokine, or cell surface marker, and a unique reporter coding sequence conjugated thereto. In this way, the readout from a particular reporter construct is a surrogate readout for cytokine, chemokine, or cell surface marker readout. Measuring readout from the reporter coding sequences described herein is in

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some instances easier than measuring cytokine or chemokine secretion, or upregulation of a cell surface marker.

In these latter embodiments, the cell line may be transfected with a number of reporter constructs each having a promoter derived from a particular cytokine, chemokine, or cell surface marker, and a unique distinguishable coding sequence conjugated thereto. In these  
5       embodiments, multiple readouts are possible from one screen. In other embodiments, multiple native readouts are also possible from one screen.

In a related embodiment, the cell may be further transfected with a nucleic acid that codes for a TLR polypeptide or a fragment thereof. Preferably, the TLR is one that is not  
10       endogenously expressed by the cell. As an example, if the cell is an RPMI 8226 cell which has been shown to express TLR7 and TLR9 according to the invention, then it may be modified to express TLRs other than these (e.g., TLR8) in some embodiments. In this aspect, the RPMI 8226 cell is responsive to TLR8 ligands. In preferred embodiments, the TLR is a human TLR (i.e., hTLR).

15       In another aspect, the invention provides an RPMI 8226 cell transfected with a TLR nucleic acid. In still another embodiment, the TLR nucleic acid is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR8, TLR10 and TLR11. The encoded TLRs nucleic acids can derive from human or non-human sources. Examples of non-human sources include, but are not limited to, murine, bovine, canine, feline, ovine,  
20       porcine, and equine species. Other species include chicken and fish, e.g., aquaculture species. The TLR nucleic acids can also include chimeric sequences consisting of domains originating from different species. In preferred embodiments, the TLR is a human TLR.

25       In still another aspect, the invention provides kits including the cells lines (e.g., the RPMI 8226 cell line), the reporter constructs and/or expression constructs described above, and instructions for use.

Other aspects of the invention provide methods for analyzing the biological activity of individual lots of material containing previously identified specific TLR ligands (i.e., specific compounds which are ligands for a particular TLR) intended for use as, or for use in the preparation of, pharmaceutical compositions. The methods permit a qualitative and,  
30       importantly, a quantitative assessment of biological activity of individual lots of TLR ligands, pre-formulation as well as post-formulation. Such methods are useful in the manufacture and validation of pharmaceutical compositions containing, as an active agent, at least one specific ligand of at least one specific TLR. The specific TLR can be any known TLR, including

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without limitation TLR3, TLR7, TLR8 and TLR9. The specific TLR ligand is an isolated TLR ligand, either found in nature or synthetic (not found in nature), including in particular certain nucleic acid molecules and small molecules. Nucleic acid molecules that are specific TLR ligands include synthetic and naturally-occurring oligonucleotides having specific base  
5 sequence motifs. Furthermore, specific TLR ligands include both agonists and antagonists of specific TLR.

These methods are to be distinguished from test procedures and acceptance criteria for new drug substances and new drug products which are classified as chemical substances. Unlike the afore-mentioned test procedures and acceptance criteria, the methods of the instant  
10 invention deal specifically with characterizing drug substances and drug products which are classified as oligonucleotides. Oligonucleotides are explicitly excluded in ICH Topic Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Step 4 – Consensus Guideline: 6 October 1999, § 1.3.

Further still, the methods of the instant invention are to be distinguished from test  
15 procedures and acceptance criteria for biotechnological/biological products. Unlike the afore-mentioned test procedures and acceptance criteria, the methods of the invention deal specifically with characterizing biotechnological/biological products which are classified as DNA products. DNA products are explicitly excluded in ICH Harmonised Tripartite Guideline Specifications: Test Procedures and Acceptance Criteria for  
20 Biotechnological/Biological Products, Step 4 – 10 March 1999, § 1.3.

In one aspect, the invention provides a method for quality assessment of a test composition containing a known TLR ligand. The method according to this aspect of the invention involves measuring a reference activity of a reference composition comprising a known TLR ligand, wherein the known TLR ligand is a nucleic acid molecule; measuring a  
25 test activity of a test composition comprising the known TLR ligand; and comparing the test activity to the reference activity. In one embodiment the method further involves the step of selecting the test composition if the test activity falls within a predetermined range of variance about the reference activity.

In one embodiment, the reference composition is a first production lot of a  
30 pharmaceutical composition comprising the known TLR ligand, and the test composition is a second production lot of a pharmaceutical composition comprising the known TLR ligand. This embodiment is particularly useful as a method for developing and applying acceptance criteria for finished pharmaceutical products containing a known TLR ligand.

In another embodiment, the reference composition is a first in-process lot of a composition comprising the known TLR ligand, and the test composition is a second in-process lot of a composition comprising the known TLR ligand. This embodiment is particularly useful as a method for developing and applying acceptance criteria for raw materials and/or other in-process materials containing a known TLR ligand bound for use in a pharmaceutical product.

In one embodiment according to this aspect of the invention, measuring the reference activity involves contacting the reference composition with an isolated cell expressing a TLR responsive to the known TLR ligand, and measuring the test activity involves contacting the test composition with the isolated cell expressing the TLR responsive to the known TLR ligand. Further, in one embodiment the isolated cell expressing the TLR responsive to the known TLR ligand includes an expression vector for the TLR responsive to the known TLR ligand. Such expression vector, and likewise for any expression vector according to the instant invention, can be introduced into the cell using any suitable method.

In one embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand naturally expresses the TLR responsive to the known TLR ligand. Such a cell can be naturally occurring or it can be a cell line, provided the cell does not include an expression vector introduced into the cell for the purpose of artificially inducing the cell to express or overexpress the TLR.

In one particular embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is RPMI 8226. In another embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is Raji, RAMOS, Nalm, THP-1 or KG-1 and the TLR is TLR9. In another embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is RPMI 8226, Raji or RAMOS and the TLR is TLR7. In yet another embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is a KG-1 cell, a Nalm cell, a Raji cell, a RAMOS cell, a Jurkat cell, a Hela cell, a Hep-2 cell, a Hep-2 cells, a A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell and the TLR is TLR3.

Further according to this aspect of the invention, in one embodiment measuring the reference activity and measuring the test activity each comprises measuring signaling activity mediated by a TLR responsive to the known TLR ligand. As described in greater detail elsewhere herein, TLR signaling involves a series of intracellular signaling events. These signaling events give rise to various downstream products, including certain transcription

factors (e.g., NF- $\kappa$ B and AP-1), cytokines, chemokines, etc., which can affect the activity of certain gene promoters. For example, in one embodiment the signaling activity is activity of a reporter gene or reporter construct under the control of a NF- $\kappa$ B response element.

In other embodiments, the signaling activity is activity of a reporter gene or reporter  
5 construct under the control of an interferon-stimulated response element (ISRE); an IFN- $\alpha$  promoter; an IFN- $\beta$  promoter; an IL-6 promoter; an IL-8 promoter; an IL-12 p40 promoter; a RANTES promoter; an IL-10 promoter or an IP-10 promoter.

In one embodiment, the known TLR ligand is an immunostimulatory nucleic acid. An immunostimulatory nucleic acid can include, without limitation, a CpG nucleic acid. In  
10 another embodiment, the known TLR ligand is an immunoinhibitory nucleic acid. When the known TLR ligand is a TLR antagonist (e.g., an immunoinhibitory oligonucleotide), the method according to this aspect of the invention can further involve measuring the reference activity of the reference composition and measuring the test activity of the test composition, each performed in the presence of a known immunostimulatory TLR ligand.

15 In various embodiments, the known TLR ligand is a ligand for a particular TLR. Thus in one embodiment the known TLR ligand is a TLR9 ligand. More specifically, in one embodiment the known TLR ligand is a CpG nucleic acid.

In one embodiment, the known TLR ligand is a TLR3 ligand. Such a ligand can include, for example, a double-stranded RNA or a homolog thereof.

20 In one embodiment, the known TLR ligand is a TLR7 ligand. In one embodiment the known TLR ligand is a TLR8 ligand.

The invention provides in another aspect a method for quality assessment of a test lot of a pharmaceutical product containing a known TLR9 ligand. The method according to this aspect of the invention involves measuring a reference activity of a reference lot of a  
25 pharmaceutical product comprising a known TLR9 ligand, wherein the known TLR9 ligand is a nucleic acid molecule; measuring a test activity of a test lot of a pharmaceutical product comprising the known TLR9 ligand; comparing the test activity to the reference activity; and rejecting the test lot if the test activity falls outside of a predetermined range of variance about the reference activity.

30 In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TGT CGT TTT GTC GTT-3' (SEQ ID NO:1).

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In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TGA CGT TTT GTC GTT-3' (SEQ ID NO:139).

5 In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TGT CGT TTT TTT CGA-3' (SEQ ID NO:140).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT CGT CGT TTC GTC GTT-3' (SEQ ID NO:141).

10 In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT CGT CGT TTT GTC GTT-3' (SEQ ID NO:142).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TTC GGT CGT  
15 TTT-3' (SEQ ID NO:143).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TTC GTG CGT TTT T-3' (SEQ ID NO:144).

In one embodiment according to this aspect of the invention, the known TLR9 ligand  
20 is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TCG GCG GCC GCC G-3' (SEQ ID NO:145).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TC\_G TTT TAC\_GGC GCC\_GTG CCG-3' (SEQ ID NO:146), wherein every internucleoside linkage is  
25 phosphorothioate except for those indicated by “\_”, which are phosphodiester.

Each of the limitations of the invention can encompass various embodiments of the invention. It is, therefore, anticipated that each of the limitations of the invention involving any one element or combinations of elements can be included in each aspect of the invention.

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### **Brief Description of the Figures**



Fig. 1 is a bar graph showing cell surface expression of various markers by RPMI 8226 24 hours and 48 hours following stimulation with CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), LPS and IL-1.

Fig. 2 is a bar graph showing IL-8 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 3 is a bar graph showing IL-6 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 4 is a bar graph showing IP-10 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 5 is a bar graph showing IL-10 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 6 is a dose response curve showing fold induction of IL-8 production 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1) and non-CpG nucleic acid (SEQ ID NO: 2). The EC<sub>50</sub> for CpG nucleic acid is 19 nM and the EC<sub>50</sub> for non-CpG nucleic acid is 263 nM.

Fig. 7 is a bar graph showing NF- $\kappa$ B activation in RPMI 8226 transfected transiently with a NF- $\kappa$ B-luciferase reporter gene construct as a function of cell density and nucleic acid amount transfected, following exposure to CpG nucleic acid (SEQ ID NO: 1), LPS and TNF- $\alpha$ . NF- $\kappa$ B activation is measured by luciferase activity.

Fig. 8 is a bar graph showing RT-PCR results from RNA isolated from RPMI 8226 using gene specific primers for TLR7, TLR8 and TLR9 genes.

Fig. 9 is a dose response curve showing IP-10 production induced by SEQ ID NO: 1, and inhibition thereof in the presence of SEQ ID NO: 151, a immunoinhibitory nucleic acid.

Fig. 10 is a bar graph showing the results of a TLR9 RT-PCR analysis of a number of cell lines.

Fig. 11 is a bar graph showing the results of a TLR7 RT-PCR analysis of a number of cell lines.

Fig. 12 is a bar graph showing the results of a TLR3 RT-PCR analysis of a number of cell lines.

Fig. 13 is a bar graph showing the results of a TLR3, TLR7, TLR8 and TLR9 RT-PCR analysis of the Raji cell line.

Fig. 14 is a graph showing IL-6 production by the Raji cell line upon stimulation with various ODN (SEQ ID NO:1; SEQ ID NO:154; SEQ ID NO:158; SEQ ID NO:160; SEQ ID  
5 NO:159; SEQ ID NO:161).

Fig. 15 is a bar graph showing IL-6 production of the Raji cell line upon stimulation with poly I:C and R-848.

Fig. 16 is a bar graph showing IFN- $\alpha$ 2 production by the Raji cell line upon stimulation with CpG ODN (SEQ ID NO: 1), R-848 and poly I:C.

Fig. 17 is a bar graph showing CD80 expression (by flow cytometry) by the RAMOS  
10 cell line upon stimulation with CpG ODN (SEQ ID NO: 1) and non-CpG ODN (SEQ ID NO: 2).

Fig. 18A is a bar graph showing the induction of NF- $\kappa$ B by 293 fibroblast cells transfected with human TLR9 in response to exposure to various stimuli, including CpG-  
15 ODN, GpC-ODN, LPS, and medium.

Fig. 18B is a bar graph showing the amount of IL-8 produced by 293 fibroblast cells transfected with human TLR9 in response to exposure to various stimuli, including CpG-ODN, GpC-ODN, LPS, and medium.

Fig. 19 is a bar graph showing the induction of NF- $\kappa$ B-luc produced by stably  
20 transfected 293-mTLR9 cells in response to exposure to various stimuli, including CpG-ODN, methylated CpG-ODN (Me-CpG-ODN), GpC-ODN, LPS and medium.

Fig. 20 is a bar graph showing the induction of NF- $\kappa$ B-luc produced by stably transfected 293-hTLR9 cells in response to exposure to various stimuli, including CpG-ODN, methylated CpG-ODN (Me-CpG-ODN), GpC-ODN, LPS and medium.

Fig. 21 is a series of gel images depicting the results of reverse transcriptase-  
25 polymerase chain reaction (RT-PCR) assays for murine TLR9 (mTLR9), human TLR9 (hTLR9), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in untransfected control 293 cells, 293 cells transfected with mTLR9 (293-mTLR9), and 293 cells transfected with hTLR9 (293-hTLR9).

30

It is to be understood that the Figures are not required for enablement of the invention.

#### **Brief Description of Sequences**

SEQ ID NO:1 is the nucleotide sequence of an immunostimulatory nucleic acid (TLR9 ligand).

SEQ ID NO:2 is the nucleotide sequence of a non-CpG nucleic acid.

SEQ ID NO:3 is the nucleotide sequence of human TLR2 cDNA (U88878).

5 SEQ ID NO:4 is the amino acid sequence of human TLR2 protein (AAC34133).

SEQ ID NO:5 is the nucleotide sequence of murine TLR2 cDNA (AF165189).

SEQ ID NO:6 is the amino acid sequence of murine TLR2 protein (NP\_036035).

SEQ ID NO:7 is the nucleotide sequence of human TLR3 cDNA (NM\_003265).

SEQ ID NO:8 is the amino acid sequence of human TLR3 protein (NP\_003256).

10 SEQ ID NO:9 is the nucleotide sequence of murine TLR3 cDNA (AF355152).

SEQ ID NO:10 is the amino acid sequence of murine TLR3 protein (AAK26117).

SEQ ID NO:11 is the nucleotide sequence of human TLR4 cDNA (U88880).

SEQ ID NO:12 is the nucleotide sequence of human TLR4 cDNA transcript variant 4 (NM\_138557).

15 SEQ ID NO:13 is the nucleotide sequence of human TLR4 cDNA transcript variant 2 (NM\_138556).

SEQ ID NO:14 is the nucleotide sequence of human TLR4 cDNA transcript variant 1 (NM\_138554).

20 SEQ ID NO:15 is the nucleotide sequence of human TLR4 cDNA transcript variant 3 (NM\_003266).

SEQ ID NO:16 is the amino acid sequence of human TLR4 protein isoform A (NP\_612564).

SEQ ID NO:17 is the amino acid sequence of human TLR4 protein isoform B (NP\_612566).

25 SEQ ID NO:18 is the amino acid sequence of human TLR4 protein isoform C (NP\_003257).

SEQ ID NO:19 is the amino acid sequence of human TLR4 protein isoform D (NP\_612567).

SEQ ID NO:20 is the nucleotide sequence of murine TLR4 cDNA (NM\_021297).

30 SEQ ID NO:21 is the nucleotide sequence of murine TLR4 mRNA (AF185285).

SEQ ID NO:22 is the nucleotide sequence of murine TLR4 mRNA (AF110133).

SEQ ID NO:23 is the amino acid sequence of murine TLR4 protein (AAD29272).

SEQ ID NO:24 is the amino acid sequence of murine TLR4 protein (AAF04278).

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- SEQ ID NO:25 is the nucleotide sequence of human TLR5 cDNA (AB060695).  
SEQ ID NO:26 is the amino acid sequence of human TLR5 protein (BAB43558).  
SEQ ID NO:27 is the amino acid sequence of human TLR5 protein (O60602).  
SEQ ID NO:28 is the amino acid sequence of human TLR5 protein (AAC34136).  
5 SEQ ID NO:29 is the nucleotide sequence of murine TLR5 cDNA (AF186107).  
SEQ ID NO:30 is the amino acid sequence of murine TLR5 protein (AAF65625).  
SEQ ID NO:31 is the nucleotide sequence of human TLR7 cDNA (AF240467).  
SEQ ID NO:32 is the nucleotide sequence of human TLR7 cDNA (AF245702).  
SEQ ID NO:33 is the nucleotide sequence of human TLR7 cDNA (NM\_016562).  
10 SEQ ID NO:34 is the amino acid sequence of human TLR7 protein (AAF60188).  
SEQ ID NO:35 is the amino acid sequence of human TLR7 protein (AAF78035).  
SEQ ID NO:36 is the amino acid sequence of human TLR7 protein (NP\_057646).  
SEQ ID NO:37 is the amino acid sequence of human TLR7 protein (Q9NYK1).  
SEQ ID NO:38 is the nucleotide sequence of murine TLR7 cDNA (AY035889).  
15 SEQ ID NO:39 is the nucleotide sequence of murine TLR7 splice variant  
(NM\_133211).  
SEQ ID NO:40 is the nucleotide sequence of murine TLR7 splice variant (AF334942).  
SEQ ID NO:41 is the amino acid sequence of murine TLR7 protein (AAK62676).  
SEQ ID NO:42 is the amino acid sequence of murine TLR7 protein (AAL73191).  
20 SEQ ID NO:43 is the amino acid sequence of murine TLR7 protein (AAL73192).  
SEQ ID NO:44 is the amino acid sequence of murine TLR7 protein (NP\_573474).  
SEQ ID NO:45 is the amino acid sequence of murine TLR7 protein (P58681).  
SEQ ID NO:46 is the nucleotide sequence of human TLR8 cDNA (AF245703).  
SEQ ID NO:47 is the nucleotide sequence of human TLR8 cDNA (AF246971).  
25 SEQ ID NO:48 is the nucleotide sequence of human TLR8 cDNA (NM\_138636).  
SEQ ID NO:49 is the nucleotide sequence of human TLR8 cDNA (NM\_016610).  
SEQ ID NO:50 is the amino acid sequence of human TLR8 protein (AAF78036).  
SEQ ID NO:51 is the amino acid sequence of human TLR8 protein (AAF64061).  
SEQ ID NO:52 is the amino acid sequence of human TLR8 protein (Q9NR97).  
30 SEQ ID NO:53 is the amino acid sequence of human TLR8 protein (NP\_619542).  
SEQ ID NO:54 is the amino acid sequence of human TLR8 protein (NP\_057694).  
SEQ ID NO:55 is the nucleotide sequence of murine TLR8 cDNA (AY035890).  
SEQ ID NO:56 is the nucleotide sequence of murine TLR8 cDNA (NM\_133212).

- SEQ ID NO:57 is the amino acid sequence of murine TLR8 protein (AAK62677).  
SEQ ID NO:58 is the amino acid sequence of murine TLR8 protein (NP\_573475).  
SEQ ID NO:59 is the amino acid sequence of murine TLR8 protein (P58682).  
SEQ ID NO:60 is the nucleotide sequence of human TLR9 cDNA (AF245704).  
5 SEQ ID NO:61 is the nucleotide sequence of human TLR9 cDNA (AB045180).  
SEQ ID NO:62 is the amino acid sequence of human TLR9 protein (AAF78037).  
SEQ ID NO:63 is the amino acid sequence of human TLR9 protein (AAF72189).  
SEQ ID NO:64 is the amino acid sequence of human TLR9 protein (AAG01734).  
SEQ ID NO:65 is the amino acid sequence of human TLR9 protein (AAG01735).  
10 SEQ ID NO:66 is the amino acid sequence of human TLR9 protein (AAG01736).  
SEQ ID NO:67 is the amino acid sequence of human TLR9 protein (BAB19259).  
SEQ ID NO:68 is the nucleotide sequence of murine TLR9 cDNA (AF348140).  
SEQ ID NO:69 is the nucleotide sequence of murine TLR9 cDNA (AB045181).  
SEQ ID NO:70 is the nucleotide sequence of murine TLR9 cDNA (AF314224).  
15 SEQ ID NO:71 is the nucleotide sequence of murine TLR9 cDNA (NM\_031178).  
SEQ ID NO:72 is the amino acid sequence of murine TLR9 protein (AAK29625).  
SEQ ID NO:73 is the amino acid sequence of murine TLR9 protein (AAK28488).  
SEQ ID NO:74 is the amino acid sequence of murine TLR9 protein (BAB19260).  
SEQ ID NO:75 is the amino acid sequence of murine TLR9 protein (NP\_112455).  
20 SEQ ID NO:76 is the nucleotide sequence of human TLR10 cDNA (AF296673).  
SEQ ID NO:77 is the amino acid sequence of human TLR10 protein (AAK26744).  
SEQ ID NO:78 is the nucleotide sequence of human TLR6 cDNA (AB020807).  
SEQ ID NO:79 is the nucleotide sequence of human TLR6 mRNA (NM\_006068).  
SEQ ID NO:80 is the amino acid sequence of human TLR6 protein (BAA78631).  
25 SEQ ID NO:81 is the amino acid sequence of human TLR6 protein (NP\_006059).  
SEQ ID NO:82 is the amino acid sequence of human TLR6 protein (Q9Y2C9).  
SEQ ID NO:83 is the nucleotide sequence of murine TLR6 cDNA (AB020808).  
SEQ ID NO:84 is the nucleotide sequence of murine TLR6 cDNA (NM\_011604).  
SEQ ID NO:85 is the nucleotide sequence of murine TLR6 cDNA (AF314636).  
30 SEQ ID NO:86 is the amino acid sequence of murine TLR6 protein (BAA78632).  
SEQ ID NO:87 is the amino acid sequence of murine TLR6 protein (AAG38563).  
SEQ ID NO:88 is the amino acid sequence of murine TLR6 protein (NP\_035734).  
SEQ ID NO:89 is the amino acid sequence of murine TLR6 protein (Q9EPW9).

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SEQ ID NO:90 is the nucleotide sequence of a consensus sequence for NF- $\kappa$ B p50 subunit.

SEQ ID NO:91 is the nucleotide sequence of a consensus sequence for NF- $\kappa$ B p65 subunit.

5        SEQ ID NO:92 is the nucleotide sequence of an example of an NF- $\kappa$ B p65 subunit binding site.

SEQ ID NO:93 is the nucleotide sequence of an example of a murine CREB binding site.

10       SEQ ID NO:94 is the nucleotide sequence of an example of a murine AP-1 binding site.

SEQ ID NO:95 is the nucleotide sequence of an example of a murine AP-1 binding site.

SEQ ID NO:96 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:97 is the nucleotide sequence of an example of an ISRE.

15       SEQ ID NO:98 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:99 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:100 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:101 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:102 is the nucleotide sequence of an example of an ISRE.

20       SEQ ID NO:103 is the nucleotide sequence of an example of an SRE.

SEQ ID NO:104 is the nucleotide sequence of an example of an SRE.

SEQ ID NO:105 is the nucleotide sequence of an example of an SRE.

SEQ ID NO:106 is the nucleotide sequence of an example of an NFAT binding site.

SEQ ID NO:107 is the nucleotide sequence of an example of an NFAT binding site.

25       SEQ ID NO:108 is the nucleotide sequence of an example of an NFAT binding site.

SEQ ID NO:109 is the nucleotide sequence of an example of an NFAT binding site.

SEQ ID NO:110 is the nucleotide sequence of an example of a GAS.

SEQ ID NO:111 is the nucleotide sequence of a p53 binding site consensus sequence.

SEQ ID NO:112 is the nucleotide sequence of an example of a p53 binding site.

30       SEQ ID NO:113 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:114 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:115 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:116 is the nucleotide sequence of an example of a p53 binding site.

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SEQ ID NO:117 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:118 is the nucleotide sequence of an example of a TARE (TNF- $\alpha$  response element).

SEQ ID NO:119 is the nucleotide sequence of an example of an SRF binding site.

5 SEQ ID NO:120 is the nucleotide sequence of an example of an SRF binding site.

SEQ ID NO:121 is the nucleotide sequence of the -620 to +50 promoter region of IFN- $\alpha$ 4.

SEQ ID NO:122 is the nucleotide sequence of the -140 to +9 promoter region of IFN- $\alpha$ 1.

10 SEQ ID NO:123 is the nucleotide sequence of the -140 to +9 promoter region of IFN- $\alpha$ 1 (point mutation, AL353732).

SEQ ID NO:124 is the nucleotide sequence of the -280 to +20 promoter region of IFN- $\beta$ .

15 SEQ ID NO:125 is the nucleotide sequence of the -397 to +5 promoter region of human RANTES (AB023652).

SEQ ID NO:126 is the nucleotide sequence of the -751 to +30 promoter region of human IL-12 p40.

SEQ ID NO:127 is the nucleotide sequence of the -250 to +30 promoter region of human IL-12 p40.

20 SEQ ID NO:128 is the nucleotide sequence of the -288 to +7 promoter region of human IL-6.

SEQ ID NO:129 is the nucleotide sequence of the IL-6 gene promoter from -1174 to +7 (M22111).

25 SEQ ID NO:130 is the nucleotide sequence of the -734 to +44 promoter region derived from human IL-8.

SEQ ID NO:131 is the nucleotide sequence of the -162 to 44 promoter region of human IL-8.

SEQ ID NO:132 is the nucleotide sequence of the -615 to +30 promoter region of human TNF- $\alpha$ .

30 SEQ ID NO:133 is the nucleotide sequence of a promoter region of human TNF- $\beta$ .

SEQ ID NO:134 is the nucleotide sequence of the -875 to +97 promoter region of human IP-10.

SEQ ID NO:135 is the nucleotide sequence of the -219 to +114 promoter region of human CXCL11 (IP-9).

SEQ ID NO:136 is the nucleotide sequence of the full length promoter region of human CXCL11 (IP-9).

5        SEQ ID NO:137 is the nucleotide sequence of the -289 to +217 promoter region of IGFBP4 (Insulin growth factor binding protein 4).

SEQ ID NO:138 is the nucleotide sequence of the full length promoter region of IGFBP4.

10        SEQ ID NO:139 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:140 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:141 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:142 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:143 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:144 is the nucleotide sequence of an immunostimulatory nucleic acid.

15        SEQ ID NO:145 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:146 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:147 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

20        SEQ ID NO:148 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

SEQ ID NO:149 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

SEQ ID NO:150 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

25        SEQ ID NO:151 is the nucleotide sequence of an immunoinhibitory nucleic acid.

SEQ ID NO:152 is the nucleotide sequence of a sense primer for human TLR3.

SEQ ID NO:153 is the nucleotide sequence of an antisense primer for human TLR3.

SEQ ID NO:154 is the nucleotide sequence of a GpC nucleic acid.

SEQ ID NO:155 is the nucleotide sequence of a CpG ODN.

30        SEQ ID NO:156 is the nucleotide sequence of a GpC ODN.

SEQ ID NO:157 is the nucleotide sequence of a Me-CpG ODN.

SEQ ID NO:158 is the nucleotide sequence of a TLR9 ligand.

SEQ ID NO:159 is the nucleotide sequence of a TLR9 ligand.



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SEQ ID NO:160 is the nucleotide sequence of a TLR9 ligand.

SEQ ID NO:161 is the nucleotide sequence of a TLR9 ligand.

### **Detailed Description of the Invention**

5 In its broadest sense, the invention relates to screening methods and tools to be used to identify and discriminate between newly discovered immunomodulatory molecules and to compare and standardize compositions of known immunomodulatory molecules. The immunomodulatory molecules are preferably TLR ligands.

10 Thus, the invention is based in part on the discovery that cell lines expressing endogenous TLR respond to TLR ligands in a manner similar to the response of peripheral blood mononuclear cells (PBMC). PBMC respond to immunomodulatory TLR ligands by modulating one or more parameters including gene expression, cell surface marker expression, cytokine and/or chemokine production and secretion, cell cycle status, phosphorylation status, and the like. TLR ligands can be categorized and distinguished based on the cellular changes they induce (i.e., their induction profiles). The ability of a TLR ligand  
15 to provide therapeutic or prophylactic benefit to a subject depends on its induction profile. The ability to screen new TLR ligands for a panel of response indicators or parameters allows for rapid discrimination and categorization of TLR ligands. Moreover, the similarity between the cell line responses and those observed after in vivo administration of the TLR ligand indicates that the cell lines are suitable predictors of in vivo activity. The use of in vitro  
20 propagated cell lines additionally overcomes the variability encountered when using freshly isolated PBMC.

The TLR ligands identified according to the invention therefore can be used therapeutically or prophylactically in a more patient- or disorder-specific manner. The  
25 invention allows for the tailoring of TLR ligands for particular patients or disorders.

The invention identifies a number of cell lines that can be used to identify TLR ligands based on endogenous TLR expression such as TLR3, TLR7 and TLR9 expression. As an example, the invention is premised in part on the discovery of TLR9 expression in a number of cell lines including RPMI 8226, Raji, RAMOS, THP-1, Nalm-6 and KG-1. Cell lines  
30 RPMI 8226, Raji and RAMOS have been determined to express TLR7 according to the invention. Cell lines KG-1 cell, a Nalm cell, a Raji cell, a RAMOS cell, a Jurkat cell, a HeLa cell, a Hep-2 cell, a Hep-2 cells, a A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell have been discovered to express TLR3 according to the invention.

It is further premised in part on the discovery that RPMI 8226 cells respond to the imidazoquinoline compound R-848. Consistent with this latter finding, it was also discovered  
5 that RPMI 8226 cells express TLR7.

The invention in other aspects provides for screening methods and tools for verifying and standardizing compositions containing known TLR ligands. These compositions may be for example commercial production lots to be used in a clinical setting. Accordingly, the invention provides methods for standardizing lots of known TLR ligands prior to distribution  
10 and use clinically. In this way, production processes can be observed and controlled and substandard production lots can be identified and eliminated prior to shipment.

The methods of the instant invention can be used at any step in the preparation and production of clinical material, i.e., pharmaceutical product. In particular, the methods will find use in characterizing or validating raw materials, in-process materials, finished product  
15 materials (e.g., pre-release materials), and post-production materials (e.g., post-release materials). The methods can also be used to validate existing process methods, as well as to validate new or changed process methods used in the production of the pharmaceutical product.

## 20 Screening Assays Generally

The screening assays provided herein may be used to identify immunomodulatory agents. Immunomodulatory agents are agents that either stimulate or inhibit immune responses in a subject. Accordingly, as used herein, immunomodulation embraces both immunostimulation and immunoinhibition.

25 The screening methods are used to identify TLR agonists and antagonists. The methods can also be used to identify compounds that enhance the immunostimulation induced by a TLR agonist. This latter set of compounds is referred to herein as "enhancers". A TLR agonist is a compound that stimulates TLR signaling activity. A TLR antagonist is a compound that inhibits TLR signaling activity. Agonists are generally referred to herein as  
30 immunostimulatory compounds because stimulation of TLR is associated with immune stimulation. Antagonists are generally referred to herein as immunoinhibitory compounds because inhibition of TLR is associated with immune inhibition. TLR antagonists include compounds that reduce (or eliminate completely) the immunostimulation induced by a TLR

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agonist. In some embodiments, the agonists, antagonists and enhancers are TLR ligands (i.e., they bind to a TLR). In other embodiments, the test compounds with agonist, antagonist or enhancer activity may act downstream or upstream of the TLR-TLR ligand interaction.

An "immunostimulatory compound" as used herein refers to a natural or synthetic compound that characteristically induces a TLR-mediated response when contacted with a suitable functional TLR polypeptide. In one embodiment the immunostimulatory compound is a natural or synthetic compound that induces a TLR-mediated response when contacted with a cell that naturally or artificially expresses a suitable functional TLR polypeptide. Depending on the aspect of the invention, the cell may be an experimental cell or a primary cell such as a PBMC.

Examples of immunostimulatory compounds include the following immunostimulatory nucleic acids, which are discussed in further detail below:

	5'-TCGTCGTTTTGTCGTTTTGTCGTT-3'	(SEQ ID NO:1)
	5'-TCGTCGTTTTGACGTTTTGTCGTT-3'	(SEQ ID NO:139)
15	5'-TCGTCGTTTTGTCGTTTTTTTCGA-3'	(SEQ ID NO:140)
	5'-TCGTCGTTTCGTCGTTTCGTCGTT-3'	(SEQ ID NO:141)
	5'-TCGTCGTTTCGTCGTTTTGTCGTT-3'	(SEQ ID NO:142)
	5'-TCGTCGTTTTTCGGTCGTTTT-3'	(SEQ ID NO:143)
	5'-TCGTCGTTTTTCGTGCGTTTTT-3'	(SEQ ID NO:144)
20	5'-TCGTCGTTTTCGGCGGCCGCCG-3'	(SEQ ID NO:145)
	5'-TCGTC_GTTTTAC_GGCGCC_GTGCCG-3'	(SEQ ID NO:146)

Imidazoquinolines are immune response modifiers thought to induce expression of several cytokines including interferons (e.g., IFN- $\alpha$  and IFN- $\beta$ ), TNF- $\alpha$  and some interleukins (e.g., IL-1, IL-6 and IL-12) as well as chemokines (e.g., IP-10 and IL-8). Imidazoquinolines are capable of stimulating a Th1 immune response, as evidenced in part by their ability to induce increases in IgG2a levels. Imidazoquinoline agents reportedly are also capable of inhibiting production of Th2 cytokines such as IL-4, IL-5, and IL-13. Some of the cytokines induced by imidazoquinolines are produced by macrophages and dendritic cells. Some species of imidazoquinolines have been reported to increase NK cell lytic activity and to stimulate B cells proliferation and differentiation, thereby inducing antibody production and secretion. Imidazoquinoline mimics can also be tested using the screening methods.

An "immunoinhibitory compound" as used herein refers to a natural or synthetic compound that characteristically inhibits a TLR-mediated response when contacted with a suitable functional TLR polypeptide. In one embodiment the immunoinhibitory compound is a natural or synthetic compound that inhibits a TLR-mediated response when contacted with a cell that naturally or artificially expresses a suitable functional TLR polypeptide.

In addition to the immunoinhibitory nucleic acids disclosed elsewhere herein, immunoinhibitory compounds and TLR antagonists encompass certain small molecules (chloroquine, quinacrine, 9-aminoacridines and 4-aminoquinolines, and derivatives thereof) described by Macfarlane and colleagues in U.S. Pat. 6,221,882; U.S. Pat. 6,399,630; U.S. Pat. 6,479,504; U.S. Pat. 6,521,637; and published U.S. Pat. application 2002/0151564, the contents of all of which are hereby incorporated by reference in their entirety.

The invention provides in part methods and tools that utilize cell lines, in modified or unmodified form, as surrogates for PBMC. Immunomodulation by TLR ligands can be assessed using one or preferably more parameters including but not limited to cytokine and chemokine secretion, upregulation of cell surface markers, changes in cell proliferation, phosphorylation changes, and the like. These parameters may be native readouts or artificial readouts as described herein.

The cellular response to immunostimulatory nucleic acids by the cell lines described herein (e.g., RPMI 8226, Raji, RAMOS, and the like) so resembles that of PBMC that these cells can be used to identify and differentiate between immunomodulatory compounds based on the extent of the induced response and the particular profile of that response. The invention provides a number of cell lines each with a particular endogenous TLR expression profile, as described herein.

The cell lines can be used to identify immunomodulatory compounds with particular response profiles. As an example, the cell lines can be used to identify molecules that are mimics to known TLR ligands. The cell lines can also be used to identify TLR ligands that trigger some but not necessarily all of the responses induced by known TLR ligands. For example, the cell line can be used to distinguish between compounds based on individual or group cytokine or chemokine secretion, or based on upregulation of one, a subset or all cell surface markers. As an example, in some therapeutic instances, it may be desirable to use a compound that induces the secretion of relatively high levels of chemokine such as IP-10, yet induces only relatively low levels of one or more other factors. The screening methods of the invention allow for the identification of such a compound with this type of induction profile.

It is to be understood that the screening method also can be used to determine effective amounts of known and newly identified immunomodulatory compounds. For example, the EC<sub>50</sub> value of a TLR ligand for the production of a particular cytokine or chemokine can be determined, thereby facilitating comparison between different nucleic acids.

5           Generally, these assays require the incubation of cells with a reference compound and a test compound, and an analysis of the readout. Depending on the embodiment, the same cells are exposed to the reference compound and the test compound. An example of this latter embodiment is a screening assay for compounds that enhance the immunostimulatory effects of a TLR agonist. Another example is a screening assay for compounds that inhibit the  
10 immunostimulatory effects of a TLR agonist. In both examples, the reference compound is a positive reference compound (i.e., it is itself immunostimulatory).

          In other embodiments, particularly those directed at identifying immunostimulatory compounds, separate aliquots from the same cell line (or from the same freshly harvested cell population) are exposed to either the reference compound or the test compound, and the  
15 readouts from each are measured and compared to the other. If the reference compound is a negative reference compound (i.e., it is inert and neither immunostimulatory nor immunoinhibitory), then any test level that is greater than the reference level is indicative of a test compound that has at least some immunostimulatory capacity. Generally, the negative reference compound is used to set background levels of immunostimulation or  
20 immunoinhibition observed in the absence of the test compound. If the reference compound is a positive reference compound (i.e., it is immunostimulatory), then it is possible to compare and contrast the induction profile of the test compound to that of the reference compound.

          In some instances, separate reference assays individually containing a positive and a negative reference compound are performed alongside the test assay. For example, if the test  
25 assay is a screen for an immunostimulatory TLR ligand, then reference assays can be a positive reference assay (in which the reference compound is immunostimulatory), a negative reference assay (in which the reference compounds is immunologically inert or neutral), or both. A test compound is defined as immunostimulatory if it induces a response greater than that of the negative reference compound. The level and profile of the immunostimulatory  
30 response can be compared to the level and profile induced by the positive reference compound. It is to be understood that a test compound that induces a level of immunostimulation less than that of the positive reference compound may still be considered immunostimulatory according to the invention. Modifications to these screening assays for a

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desired readout will be apparent to those of ordinary skill in the art based on the teachings provided herein.

If the test assay is a screen for an immunoinhibitory TLR ligand, then the assay may generally involve co-incubation of the test compound and a positive reference compound.

5 The control assay may include co-incubation of the negative and positive reference compounds. As used herein, co-incubation embraces simultaneous or consecutive addition of the reference and test compounds. The test compound may be added before or after the positive reference compound. An immunoinhibitory test compound may be identified by a diminution of the immunostimulatory response induced by the positive reference compound  
10 when in the presence of the test compound. If the level of the response is less in the presence of the test compound, this indicates that the test compound is capable of interfering with the immunostimulatory effects of the positive reference compound. As an example, simultaneous or consecutive addition of a putative immunoinhibitory test compound can reduce the amount of cytokines or chemokines secreted by cells in response to the positive reference compound  
15 alone, indicating an inhibition of the immunostimulatory effects of the positive reference compound.

The reference immunoinhibitory compound can be used at one or more concentrations in conjunction with a selected or constant concentration of reference immunostimulatory compound. Under proper conditions, the immunostimulatory effect of the reference  
20 immunostimulatory compound will be less in the presence of the immunoinhibitory substance than in the absence of the immunoinhibitory substance. Furthermore, under proper conditions, the immunostimulatory effect of the reference immunostimulatory compound will decrease with increasing concentration of the immunoinhibitory substance.

The breadth of response by the cell line to immunomodulatory compounds, and its  
25 facile manipulation, allows for the identification of novel compounds. The cell line allows the rapid discovery of such compounds given that it lends itself to high throughput screening methods such as those provided herein. These methods and compositions are described in greater detail below. The invention therefore provides screening methods that utilize cell lines that either endogenous express TLRs such as the RPMI 8226 cell line as well as cell  
30 lines that have been modified to express TLRs. The invention further provides compositions that comprise such cell lines.

The verification and standardization methods of the invention generally involve assays in which an isolated cell expressing a functional TLR is contacted with each of two

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compositions, each composition containing a known ligand for the TLR. One composition is a reference composition, and the assay using the reference composition yields a reference activity. The second composition is a test composition, and the assay using the test composition yields a test activity. The two contacting steps can be performed on separate cells that are alike, and typically will be performed on separate populations of cells that are alike. For example, the separate cells or the separate populations of cells can be drawn from a single population of cells. In typical usage according to this embodiment, the reference and test activities are measured essentially concurrently, although the use of historical reference activity is also contemplated by the methods of the invention. As an alternative, the two contacting steps can be performed on a single cell or on a single population of cells, usually in an essentially concurrent manner when it is desirable to have competition between reference and test compositions. In one embodiment the known TLR ligand is a nucleic acid molecule.

The assays of the invention are performed under specific conditions so that comparison can be made between reference and test activities or levels. The results of the comparison can be used as a basis upon which to accept or reject the test material as suitable for its intended use.

The biological characterization of the reference composition will generally entail a series of biological activity measurements of the reference composition using a single assay under defined conditions in order to define a range of inter-test variance. The range of inter-test variance so obtained using reference composition can be used to define an acceptable range of variance within which a subsequent test measurement must fall in order to satisfy quality standards. Such a range of acceptable variance can serve as a basis for developing predetermined range of variance about the reference activity, i.e., acceptance criteria for a particular test composition or test lot. For example, a particular reference composition can be assayed under defined conditions in a number of independent measurements and found to yield a result expressed as  $100 \pm 5$  units of activity. Under this same example, a subsequent test measurement of a test composition performed using the same assay and defined conditions is found to yield 97 units of activity. The activity of the test composition under this example thus yielded a result that falls within the normal range of inter-test variance observed for the reference composition. Accordingly, the test material under this example could be selected on the basis of the test activity falling within a predetermined range of variance about the reference activity. In short, the test material can be deemed acceptable

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provided the test activity falls within a predetermined range of activity that is related to the activity of the reference material.

In one embodiment, the methods of the invention provide for comparison between a reference lot of a particular TLR ligand and a test lot of the same particular TLR ligand. Such  
5 comparison is useful for quality control assessment of the test lot of material, also referred to herein as validation, e.g., product validation. Such comparison is also useful for process validation.

In another embodiment, the methods of the invention provide for comparison between a reference lot of a particular TLR ligand and a test lot of a different TLR ligand. In a simple  
10 example, where a test TLR ligand (T) is expected to have little or no activity characteristic of reference TLR ligand (R), comparison can be made between T and R to confirm the lack of R-like activity possessed by T. In a more complex example, where a test TLR ligand (C) is capable of exerting two different effects, wherein each effect is characteristic of one of two different classes of TLR ligand and is best characterized by one of two different reference  
15 TLR ligands (A and B), the test TLR ligand (C) can be compared with either of the two reference TLR ligands (A or B). In this second example, test composition C could be found, for example, to possess 50 percent A-like activity compared with reference A and 70 percent B-like activity compared with reference B. Test composition C could thus independently meet or fail to meet predetermined standards for each of A-like activity and B-like activity.  
20 Such comparison is also useful for quality control assessment of the test lot of material, e.g., product validation. Of course test TLR ligand C can alternatively or additionally be compared against reference TLR ligand C, as described in the preceding paragraph.

To facilitate the methods of the invention, certain conditions for carrying out the assays are standardized and used for measurements of both reference activity and test activity.  
25 In this way direct comparison between reference activity and test activity can be made readily. Conditions that can be standardized and used in this manner can include, without limitation, readout, temperature, media characteristics, duration (time between introduction of reference composition or test composition and activity measurement), methods of sampling, etc. In some embodiments the methods of the invention can be at least partially automated in order to  
30 increase throughput and/or to reduce inter-test variability. For example, robotic devices and workstations with the capacity to dispense and/or sample fluids in a set or programmable fashion are now well known in the art and can be used in performing the methods of the instant invention.



In one embodiment a standard curve of reference composition activity is employed. Typically the standard curve is generated by selecting conditions including concentration of the reference composition such that the dose-response curve is essentially linear (and the slope is non-zero) over a range of concentrations that includes the effective concentration at which activity is 50 percent of maximum (EC50). In one embodiment the standard curve spans a range of concentrations defined by  $EC50 \pm 1 \log$  concentration, e.g.,  $1 \times 10^{-7} \text{ M} - 1 \times 10^{-5} \text{ M}$ , where EC50 is  $1 \times 10^{-6} \text{ M}$ . In another embodiment the standard curve spans a broader range of concentrations defined by  $EC50 \pm 2 \log$  concentration, e.g.,  $1 \times 10^{-8} \text{ M} - 1 \times 10^{-4} \text{ M}$ , where EC50 is  $1 \times 10^{-6} \text{ M}$ . In yet another embodiment the standard curve spans a narrower range of concentrations defined by  $EC50 \pm 0.5 \log$  concentration, e.g.,  $3.16 \times 10^{-7} \text{ M} - 3.16 \times 10^{-6} \text{ M}$ , where EC50 is  $1 \times 10^{-6} \text{ M}$ . The foregoing embodiments are intended to be exemplary and not limiting in any way. One of skill in the art will be able to select, for a given reference composition and without undue experimentation, an appropriate range of concentrations about some middle value in order to generate an essentially linear standard curve with a non-zero slope.

In one embodiment a non-linear standard curve of reference and test composition activity is employed. The standard curve can be generated by selecting conditions including concentrations of the reference composition such that the dose-response curve is sigmoidal and the EC50 value can be determined. Comparison of reference and test activity can be done by comparing, e.g., the EC50 values of both curves. Concentration range is chosen to yield a complete sigmoidal response, e.g., concentration should include  $EC50 \pm 3 \log$  concentration or  $EC50 \pm 4 \log$  concentration. In the case of testing an inhibitory compound the value determined would be the IC50, i.e., concentration where inhibition of the stimulatory signal is half-maximal.

The methods of the invention can be adapted to be automated or at least partially automated methods, as well as to parallel array or high throughput format methods. For example, the assays can be set up using multiwell plates in which cells are dispensed in individual wells and reagents are added in a systematic manner using a multiwell delivery device suited to the geometry of the multiwell plate. Manual and robotic multiwell delivery devices suitable for use in a high throughput screening assay are known by those skilled in the art. Each well or array element can be mapped in a one-to-one manner to a particular test condition, such as the test compound. Readouts can also be performed in this multiwell array, preferably using a multiwell plate reader device or the like. Examples of such devices are

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known in the art and are available through commercial sources. Sample and reagent handling can be automated to further enhance the throughput capacity of the screening assay, such that dozens, hundreds, thousands, or even millions of parallel assays can be performed in a day or in a week. Fully robotic systems are known in the art for applications such as generation and analysis of combinatorial libraries of synthetic compounds. See, for example, U.S. Pat. Nos. 5,443,791 and 5,708,158.

#### Cell lines

The screening methods may use experimental cells. As used herein, an experimental cell is a non-primary cell (i.e., it is not a cell that has been recently harvested from a subject). It excludes, for example, freshly harvested PBMCs. An experimental cell includes a cell from a cell line such as the RPMI 8226 cell line.

In certain embodiments, the cell naturally expresses a functional TLR. In one embodiment relating to the verification and standardization aspects of the invention, the cell may be a PBMC, preferably a PBMC freshly harvested from a subject.

Cells that would be suitable for identification of TLR agonists, antagonists or enhancers according to the invention may possess one or more particular attributes. These attributes include but are not limited to being of human origin, being an immortalized stable cell line, endogenously expressing at least one functional TLR or a combination of functional TLRs, having intact signaling mechanisms, having intact uptake mechanisms, being able to upregulate cytokines, chemokines or cell surface markers, deriving from normal human B cells or from myeloma or B cell leukemia, deriving from human plasmacytoid and myeloid dendritic cells, and readily activatable by TLR ligands such as TLR7 ligands, TLR8 ligands or TLR9 ligands such as CpG nucleic acids or nucleic acids having other immunostimulatory sequence motifs or small molecules such as imidazoquinoline compounds.

In some embodiments, the cell line is the Raji cell line which expresses TLR3, TLR7 and TLR9. This latter cell line secretes, for example, IL-6 and IFN- $\alpha$ 2 upon CpG nucleic acid exposure. In other embodiments, the cell line is RPMI 8226 which expresses TLR7 and TLR9. Upon CpG nucleic acid exposure, this cell line expresses, produces and/or secretes IL-8, IL-10, IP-10 and TNF- $\alpha$ . It also expresses at its cell surface CD86, HLA-DR and CD71. In yet other embodiments, the cell line is the RAMOS cell line which expresses TLR3, TLR7 and TLR9. This cell line at least induces CD80 cell surface expression in response to CpG nucleic acid exposure.

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The cell lines have been observed to respond in a concentration dependent manner to TLR ligands such as but not limited to CpG nucleic acids and some non-CpG nucleic acids including T-rich nucleic acids, poly-T nucleic acids and poly-G nucleic acids. The highest responses have been observed using CpG nucleic acids.

5       The screening methods employ a variety of cell lines as shown in the Examples. These include A549 (human lung carcinoma, ATCC CCL-185), BeWo (human choriocarcinoma, ATCC CCL-98), HeLa (human cervix carcinoma, ATCC CCL-2), Hep-2 (human cervix carcinoma, ATCC CCL-23), KG-1 (human acute myeloid leukemia, ATCC CCL-246), MUTZ-3 (human acute myelomonocytic leukemia, German Collection of Cell  
10 lines and Microorganisms (DSZM) ACC-295), Nalm-6 (human B cell precursor leukemia, DSZM ACC-128), NK-92 (human Natural killer cell line, ATCC CRL-2407), NK-92 MI (IL-2 independent human Natural killer cell line, ATCC CRL-2408), Raji (human B lymphocyte Burkitt's lymphoma, ATCC CCL-86), RAMOS (B lymphocyte Burkitt's lymphoma, ATCC CRL-1596), RPMI 8226 (human B lymphocyte multiple myeloma, ATCC CCL-155), THP-1  
15 (human acute monocytic leukemia, ATCC TIB 202), U937 (human lymphoma, ATCC CRL-1593.2) and Jurkat (human T cell leukemia, ATCC TIB 152).

As shown in the Examples, each of the afore-mentioned cell lines has a particular endogenous TLR expression profile which dictates its suitability in a particular screening assay.

20       A cell that artificially expresses a functional TLR can be a cell that does not express the functional TLR but for a transfected TLR expression vector. For example, human 293 fibroblasts (ATCC CRL-1573) do not express TLR7, TLR8 or TLR9, and they express very little TLR3. As described in the examples below, such cells can be transiently or stably transfected with suitable expression vector (or vectors) so as to yield cells that do express  
25 TLR3, TLR7, TLR8, TLR9, or any combination thereof. Alternatively, a cell that artificially expresses a functional TLR can be a cell that expresses the functional TLR at a significantly higher level with the TLR expression vector than it does without the TLR expression vector. Transfected cells are considered modified cells, as used herein.

30       A cell that artificially expresses an expression or reporter construct is preferably stably transfected.

RPMI

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The RPMI 8226 cell line is a human multiple myeloma cell line. The cell line was established from the peripheral blood of a 61 year old man at the time of diagnosis for multiple myeloma (IgG lambda type). RPMI 8226 was previously reported as responsive to CpG nucleic acids as evidenced by the production and secretion of IL-6 protein and production of IL-12p40 mRNA. (Takeshita et al. (2000), *Eur. J. Immunol.* 30, 108-116, and Takeshita et al. (2000) *Ibid.* 30, 1967-1976) Takeshita et al. however used the cell line solely to study promoter constructs in order to identify transcription factor binding sites important for CpG nucleic acid signaling. It is now known according to the invention that the cell line produces a number of other chemokines and cytokines including IL-8, IL-10 and IP-10. It has also been discovered according to the invention that the cell line responds to immunostimulatory nucleic acids by upregulating cell surface expression of particular markers. Many of these markers, including CD71, CD86 and HLA-DR, are similarly upregulated in PBMCs exposed to immunostimulatory nucleic acids. This has been observed using flow cytometric analysis of the cell line following CpG nucleic acid exposure. In other aspects of the invention, the cell line can be used in similar screening assays that involve secretion of IL-6, IL-12 and/or TNF- $\alpha$ .

It has recently been discovered that R-848 mediates its immunostimulatory effects via other TLR family members, namely TLR7 and TLR8. TLR7 has previously been found expressed on human B cells. It has now also been discovered according to the invention that RPMI 8226 expresses TLR9 as well as TLR7, thus making it a suitable cell line for identifying immunostimulatory nucleic acid and/or imidazoquinoline (e.g., R-848) mimics or other small molecules that also signal through TLR7 and/or TLR9. Incubation of RPMI 8226 cells with the imidazoquinoline R-848 (Resiquimod) induces for example IL-8, IL-10 and IP-10 production.

#### Known TLR Ligands

Ligands for many but not all of the TLRs have been described. For instance, it has been reported that TLR1 and TLR2 signals in response to peptidoglycan and lipopeptides. Yoshimura A et al. (1999) *J Immunol* 163:1-5; Brightbill HD et al. (1999) *Science* 285:732-6; Aliprantis AO et al. (1999) *Science* 285:736-9; Takeuchi O et al. (1999) *Immunity* 11:443-51; Underhill DM et al. (1999) *Nature* 401:811-5. TLR4 has been reported to signal in response to lipopolysaccharide (LPS). Hoshino K et al. (1999) *J Immunol* 162:3749-52; Poltorak A et al. (1998) *Science* 282:2085-8; Medzhitov R et al. (1997) *Nature* 388:394-7. Bacterial

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flagellin has been reported to be a natural ligand for TLR5. Hayashi F et al. (2001) *Nature* 410:1099-1103. TLR6, in conjunction with TLR2, has been reported to signal in response to proteoglycan. Ozinsky A et al. (2000) *Proc Natl Acad Sci USA* 97:13766-71; Takeuchi O et al. (2001) *Int Immunol* 13:933-40.

5 TLR9 is a receptor for CpG DNA. Hemmi H et al. (2000) *Nature* 408:740-5. Other TLR9 ligands are described herein under "Immunostimulatory Nucleic Acids". Certain imidazoquinoline compounds having antiviral activity are ligands of TLR7 and TLR8. Imidazoquinolines are potent synthetic activators of immune cells with antiviral and antitumor properties. R-848 is a ligand for human TLR7 and TLR8. Jurk M et al. (2002) *Nat Immunol*  
10 3:499. Ligands of TLR3 include poly(I:C) and double-stranded RNA (dsRNA). Alexopoulou et al. (2001) *Nature* 413:732-738. For purposes of this invention, poly(I:C) and double-stranded RNA (dsRNA) are classified as oligonucleotide molecules. TLR3 may have a role in host defense against viruses.

#### 15 Reference and Test Compounds

A test and/or reference compound can be a nucleic acid such as an oligonucleotide or a polynucleotide, an oligopeptide, a polypeptide, a lipid such as a lipopolysaccharide, a carbohydrate such as an oligosaccharide or a polysaccharide, or a small molecule. Alternatively, these compounds may also comprise or be synthesized from elements such as  
20 amino acids, carbohydrates, hormones, lipids, organic molecules, and the like.

Small molecules in general include naturally occurring, synthetic, and semisynthetic organic and organometallic compounds with molecular weight less than about 2.5 kDa. Examples of small molecules include most drugs, subunits of polymeric materials, and analogs and derivatives thereof.

25 Some specific examples of small molecules include the imidazoquinolines. As used herein, an imidazoquinolines include imidazoquinoline amines (imidazoquinolinamines), imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, and 1,2 bridged imidazoquinoline amines. These compounds have been described in U.S. Pat. Nos. 4,689,338; 4,929,624; 5,238,944; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,389,640;  
30 5,395,937; 5,482,936; 5,494,916; 5,525,612; 6,039,969 and 6,110,929. Particular species of imidazoquinoline agents include resiquimod (R-848; S-28463; 4-amino-2 ethoxymethyl- $\alpha,\alpha$ -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol); and imiquimod (R-837; S-26308; 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline-4-amine). Further examples of specific small

molecules include 4-aminoquinoline and derivatives thereof, 9-aminoacridine and derivatives thereof, and additional compounds disclosed in U.S. Pat. Nos. 6,221,882; 6,399,630; 6,479,504; and 6,521,637; and published U.S. Pat. Application No. 2002/0151564 A1, the entire contents of which are hereby incorporated by reference.

5           The test and reference compounds may be formulated for pharmaceutical use or not. For example, a test compound not formulated for pharmaceutical use can be a compound (e.g., a lot or batch of the compound) under evaluation for possible use in preparing a pharmaceutical formulation of the compound.

          A reference compound, as used herein, is a compound having a known activity in the presence of a TLR. The reference compound may stimulate TLR signaling (and is therefore regarded as a positive reference compound), or it may be inert in the presence of a TLR (and is therefore regarded as a negative reference compound). If it is a positive reference compound, it need not be the best known stimulator of TLR signaling (i.e., it is possible that other reference compounds and even test compounds will stimulate TLR signaling to a greater extent). The readout of the screening assay may simply be stated relative to the level of signaling that occurs in the presence of the reference compound. Preferably, the reference compound is analyzed prior to the screening assay in order to determine its level of activity on a TLR. In some aspects of the invention, the reference compound and the test compound will be assayed separately (i.e., in separate wells); in other aspects, the reference compound and the test compound will be assayed together (i.e., in the same well). These latter aspects are designed to measure the ability of a test compound to modulate the activity of the reference compound. The activity of the test compound and the reference compound combined (i.e., when assayed together in the same well) may be the same as that of the positive reference compound alone, indicating at a minimum that the test compound is not inhibitory; or it may be less than that of the positive reference compound, indicating at a minimum that it is inhibitory to the effect of the reference compound; or it may be additive or synergistic possibly indicating that the test compound is an enhancer. The effect of an enhance may be due to its ability to stimulate TLR signaling independently of the positive reference compound.

30           A "reference composition" as used herein refers to a composition that includes a reference compound and optionally another agent, e.g., a pharmaceutically acceptable carrier and/or another biologically active agent. A reference compound may be an immunostimulatory compound or it may be an immunoinhibitory compound.

As discussed further below, in some aspects of the invention the reference compositions include both finished products, e.g., finished pharmaceutical products, as well as raw materials and other in-process materials used for the preparation of such finished products, all of which contain a known TLR ligand. As used herein, a “production lot” shall refer to a batch or lot of a completed product prepared for release as clinical material, e.g., a pharmaceutical product. As used herein, an “in-process lot” shall refer to a batch or lot of unfinished product that is prepared in the course of making a production lot; an “in-process lot” shall also refer to a batch or lot of raw material provided for use in the production of a production lot.

In some aspects of the invention, the reference compositions of the invention are highly characterized in terms of their chemical, physical, and biological properties. A reference composition will be a specific composition previously determined to have a specific activity, or range of specific activity, of the particular known TLR ligand present in the composition. As used herein, “specific activity” refers to an amount of activity per unit mass or per unit volume of the reference composition as a whole, as determined using a defined assay under defined conditions. In one embodiment the reference composition is a representative sample of a particular lot or batch of a specific TLR ligand. In one embodiment the reference composition is a representative sample of a particular lot or batch of a specific TLR ligand formulated for pharmaceutical use, e.g., a sterile solution of the TLR ligand at a determined concentration or activity.

At least the following parameters are typically very well defined for a given reference composition: chemical formula of the active ingredient TLR ligand (e.g., nucleobase sequence and type of backbone of a nucleic acid; structural formula of a small molecule); concentration; diluent composition; and purity. Such parameters as purity and concentration can be determined using any appropriate physicochemical method, e.g., optical spectroscopy including absorbance at one or more specified wavelengths; nuclear magnetic resonance (NMR) spectroscopy; mass spectrometry (MS), including matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS); melting point; specific gravity; chromatography including as appropriate high pressure liquid chromatography (HPLC), one- and two-dimensional polyacrylamide gel electrophoresis (PAGE), capillary electrophoresis, and the like; as well as other methods known to those of skill in the art.

Reference compositions can also be very well characterized in terms of their biological activity, independent of the methods of the invention, although the methods of the

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invention generally include such characterization, at least in part. A reference composition can be very well characterized in terms of its biological activity by characterizing, both qualitatively and quantitatively, the response by sensitive cells to the reference composition under defined conditions. For example, a reference composition can be a specific CpG oligonucleotide such as SEQ ID NO:1 which in a specific assay and under specific conditions of temperature, concentration, duration of contact between the CpG oligonucleotide and a population of TLR9-expressing cells, and particular readout, reliably yields a specific result or range of results. Results can be expressed in any suitable manner, but can include results expressed on a per-cell basis, e.g., picograms of particular cytokine per cell per hour of contact with the reference composition. Reference compositions can be very well characterized in terms of their biological activity according to one or more parameters, for example, according to their capacity to induce each of a plurality of cytokines.

The methods of the invention also involve measurement of a test activity of a test composition containing a known TLR ligand. A "test composition" as used herein refers to a composition that includes a test compound and optionally another agent, e.g., a pharmaceutically acceptable carrier and/or another biologically active agent. A test compound can be an immunostimulatory compound or it can be an immunoinhibitory compound. In some aspects of the invention, the test compound is a known TLR ligand. Test compositions of the invention may comprise known TLR agonist or TLR antagonist compounds, generally but not necessarily nominally the same as the reference compositions against which comparison is to be made according to some aspects of the invention. Thus test compositions may encompass immunostimulatory compounds, immunoinhibitory compounds, known TLR ligands, finished pharmaceutical products, and raw materials and other in-process materials used for the preparation of such finished products.

Unlike a reference composition, a test composition is not characterized at all, or is only partially characterized, or is not as well characterized as the reference composition, in terms of its chemical, physical, or (most particularly) biological properties. The methods of the invention permit further characterization of the test composition by comparison with a reference composition. In some aspects, a test composition will be a specific composition previously determined to be a ligand of a specific TLR. In one embodiment the test composition is a representative sample of a particular lot or batch of a specific TLR ligand. In one embodiment the test composition is a representative sample of a particular lot or batch of



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a specific TLR ligand formulated for pharmaceutical use, e.g., a sterile solution of the TLR ligand at a determined concentration or activity.

#### Immunostimulatory and Immunoinhibitory Nucleic Acids

5 Nucleic acids useful as reference compounds and as test compounds in the methods of the invention include single- and double-stranded natural and synthetic nucleic acids, including those with phosphodiester, stabilized, and chimeric backbones. Also encompassed are at least the following classes of nucleic acids, which are described in detail below: immunostimulatory CpG nucleic acids (CpG nucleic acids), including but not limited to types  
10 A, B, and C; immunostimulatory non-CpG nucleic acids, including without limitation methylated CpG nucleic acids, T-rich nucleic acids, TG-motif nucleic acids, CpI motif nucleic acids, and poly-G nucleic acids; and immunoinhibitory nucleic acids. Nucleic acids useful as reference compounds and as test compounds in the methods of the invention also include nucleic acids with modified backbones, including "soft" and "semi-soft" oligonucleotides as  
15 described herein. As will be appreciated from the descriptions below, certain of these various classes of nucleic acids can coexist in a given nucleic acid molecule.

A "nucleic acid" as used herein with respect to test compounds and reference compounds used in the methods of the invention, shall refer to any polymer of two or more individual nucleoside or nucleotide units. Typically individual nucleoside or nucleotide units  
20 will include any one or combination of deoxyribonucleosides, ribonucleosides, deoxyribonucleotides, and ribonucleotides. The individual nucleotide or nucleoside units of the nucleic acid can be naturally occurring or not naturally occurring. For example, the individual nucleotide units can include deoxyadenosine, deoxycytidine, deoxyguanosine, thymidine, and uracil. In addition to naturally occurring 2'-deoxy and 2'-hydroxyl forms,  
25 individual nucleosides also include synthetic nucleosides having modified base moieties and/or modified sugar moieties, e.g., as described in Uhlmann E et al. (1990) *Chem Rev* 90:543-84. The linkages between individual nucleotide or nucleoside units can be naturally occurring or not naturally occurring. For example, the linkages can be phosphodiester, phosphorothioate, phosphorodithioate, phosphoramidate, as well as peptide linkages and other  
30 covalent linkages, known in the art, suitable for joining adjacent nucleoside or nucleotide units. The linkages can also be mixed in a single polymer (e.g., a semi-soft backbone). The nucleic acid test compounds and nucleic acid reference compounds typically range in size from 3-4 units to a few tens of units, e.g., 18-40 units.

In some embodiments the nucleic acids are oligonucleotides made up of 2 to about 100 nucleotides, and more typically 4 to about 40 nucleotides. Oligonucleotides composed exclusively of deoxynucleotides are termed oligodeoxyribonucleotides or, equivalently, oligodeoxynucleotides (ODN).

5 A CpG nucleic acid is an immunostimulatory nucleic acid which contains a cytosine-guanine (CG) dinucleotide, the C residue of which is unmethylated. The effects of CpG nucleic acids on immune modulation have been described extensively in U.S. Pat. Nos. 6,194,388; 6,207,646; 6,214,806; 6,218,371; 6,239,116; and 6,339,068; and published patent applications, such as PCT/US95/01570 (WO 96/02555); PCT/US98/04703 (WO 98/40100);  
10 and PCT/US99/09863 (WO 99/56755). The entire contents of each of these patents and published patent applications is hereby incorporated by reference. The entire immunostimulatory nucleic acid can be unmethylated or portions can be unmethylated, but at least the C of the 5'-CG-3' must be unmethylated. The CpG nucleic acid sequences of the invention include, without limitation, those broadly described above as well as those disclosed  
15 in U.S. Pat. Nos. 6,207,646 and 6,239,116.

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' (SEQ ID NO:1).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTGACGTTTTGTCGTT-3' (SEQ ID NO:139).

20 In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTGTCGTTTTTTTCGA-3' (SEQ ID NO:140).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTCGTCGTTTCGTCGTT-3' (SEQ ID NO:141).

In one embodiment the CpG nucleic acid has a base sequence provided by  
25 5'-TCGTCGTTTCGTCGTTTGTGTCGTT-3' (SEQ ID NO:142).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTTCGGTCGTTTT-3' (SEQ ID NO:143).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTTCGTGCGTTTT-3' (SEQ ID NO:144).

30 In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTCGGCGGCCCGCCG-3' (SEQ ID NO:145).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTC\_GTTTTAC\_GGCGCC\_GTGCCG-3' (SEQ ID NO:146).

The oligonucleotides described by SEQ ID NOs: 1, 139-145 are fully stabilized phosphorothioate backbone ODN. The oligonucleotide of SEQ ID NO:146 has a chimeric backbone in which all internucleoside linkages are phosphorothioate except for those indicated by “\_”, which are phosphodiester.

5 CpG nucleic acids have been further classified by structure and function into at least the following three types, all of which are intended to be encompassed within the methods of the instant invention: Type B CpG nucleic acids such as SEQ ID NO:1 include the earliest described CpG nucleic acids and characteristically activate B cells but do not induce or only weakly induce expression of IFN- $\alpha$ . Type B nucleic acids are described in U.S. Patents  
10 6,194,388; 6,207,646; 6,214,806; 6,218,371; 6,239,116; and 6,339,068. Type A CpG nucleic acids, described in published international application PCT/US00/26527 (WO 01/22990), incorporate a CpG motif, include a hybrid phosphodiester/phosphorothioate backbone, and characteristically induce plasmacytoid dendritic cells to express large amounts of IFN- $\alpha$  but do not activate or only weakly activate B cells. Type C oligonucleotides incorporate a CpG,  
15 include a chimeric backbone, include a GC-rich palindromic or nearly-palindromic region, and are capable of both activating B cells and inducing expression of IFN- $\alpha$ . These have been described, for example, in copending U.S. Pat. application Ser. No. 10/224,523, filed August 19, 2002. Exemplary sequences of A, B and C class nucleic acids are described in the afore-mentioned references, patents and patent applications, the entire contents of which are  
20 hereby incorporated by reference herein.

In other embodiments of the invention, a non-CpG nucleic acid is used. A non-CpG nucleic acid is an immunostimulatory nucleic acid which either does not have a CpG motif in its sequence, or has a CpG motif which contains a methylated C residue. In some instances, the non-CpG nucleic acid may still be immunostimulatory by virtue of its having other  
25 immunostimulatory motifs such as those described herein and known in the art. In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid. In some instances the non-CpG nucleic acid is still immunostimulatory despite methylation of the C of the CpG motif, even without having another non-CpG immunostimulatory motif described herein and known in the art.

30 In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-TZGTZGTTTTGTZGTTTTGTZGTT-3' (SEQ ID NO:147), wherein Z represents 5-methylcytosine.

In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-TZGTZGZTGTZTZZGZTTZTTZTTGZZ-3' (SEQ ID NO:148), wherein Z represents 5-methylcytosine.

5 In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-GZGTTTGZTZTTZTTZTTGZG-3' (SEQ ID NO:149), wherein Z represents 5-methylcytosine.

In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-GZZZAAGZTGGZATZZGTZA-3' (SEQ ID NO:150), wherein Z represents 5-methylcytosine.

10 Non-CpG nucleic acids include T-rich immunostimulatory nucleic acids. The T-rich immunostimulatory nucleic acids include those disclosed in published PCT patent application PCT/US00/26383 (WO 01/22972), the entire contents of which are incorporated herein by reference. In some embodiments, T-rich nucleic acids 24 bases in length are used. A T-rich nucleic acid is a nucleic acid which includes at least one poly T sequence and/or which has  
15 nucleotide composition of greater than 25% T nucleotide residues. A nucleic acid having a poly-T sequence includes at least four Ts in a row, such as 5'-TTTT-3'. In some embodiments the T-rich nucleic acid includes more than one poly T sequence. In important embodiments, the T-rich nucleic acid may have 2, 3, 4, or more poly T sequences, such as SEQ ID NO:1.

Non-CpG nucleic acids also include poly-G immunostimulatory nucleic acids. A  
20 variety of references describe the immunostimulatory properties of poly-G nucleic acids. Pisetsky DS et al. (1993) *Mol Biol Reports* 18:217-221; Krieger M et al. (1994) *Ann Rev Biochem* 63:601-637; Macaya RF et al. (1993) *Proc Natl Acad Sci USA* 90:3745-3749; Wyatt JR et al. (1994) *Proc Natl Acad Sci USA* 91:1356-1360; Rando and Hogan, 1998, In *Applied Antisense Oligonucleotide Technology*, Krieg and Stein, eds., pp. 335-352; Kimura Y et al.  
25 (1994) *J Biochem (Tokyo)* 116:991-994.

The immunostimulatory nucleic acids of the invention can also be those which do not possess CpG, methylated CpG, T-rich, or poly-G motifs.

Exemplary immunostimulatory nucleic acid sequences include but are not limited to those immunostimulatory sequences described and listed in U.S. Non-Provisional Pat.  
30 Application No. 09/669,187, filed on September 25, 2000, and in corresponding published PCT patent application PCT/US00/26383 (WO 01/22972).

Immunoinhibitory nucleic acids have been described in Lenert P et al. (2001) *Antisense Nucleic Acid Drug Dev* 11:247-56 and in Stunz L et al. (2002) *Eur J Immunol*

32:1212-22. These inhibitory phosphorothioate ODN (S-ODN) differ from stimulatory S-ODN by having 2-3 G substitutions in the central motif. As inhibitory S-ODN did not directly interfere with the NF- $\kappa$ B DNA binding but prevented CpG-induced NF- $\kappa$ B nuclear translocation of p50, p65, and c-Rel and blocked p105, I $\kappa$ B $\alpha$ , and I $\kappa$ B $\beta$  degradation, Lenert et al. suggested that the putative target of immunoinhibitory ODN would lie upstream of inhibitory kinase (IKK) activation. Stunz et al. reported that replacing GCGTT or ACGTT with GCGGG or ACGGG converted a stimulatory 15-mer ODN into an inhibitory ODN. All inhibitory ODN had three consecutive G, and a fourth G increased inhibitory activity, but a deazaguanosine substitution to prevent planar stacking did not affect activity. Inhibitory ODN blocked apoptosis protection and cell-cycle entry induced by stimulatory ODN, but not that induced by lipopolysaccharide, anti-CD40 or anti-IgM+IL-4. ODN-driven up-regulation of cyclin D(2), c-Myc, c-Fos, c-Jun and Bcl(XL) and down-regulation of cyclin kinase inhibitor p27(kip1) were all blocked by inhibitory ODN. Stunz et al. also reported that interference with uptake of stimulatory ODN did not account for the inhibitory effects of the immunoinhibitory nucleic acids.

In one embodiment the immunoinhibitory nucleic acid has a base sequence provided by 5'-TCCTGGCGGGGAAGT-3' (SEQ ID NO:151).

Immunoinhibitory nucleic acids have also been described in U.S. Pat. No. 6,194,388, issued to Krieg et al. The immunoinhibitory oligonucleotides disclosed by Krieg et al. are oligonucleotides with GCG trinucleotides at or near the ends of the oligonucleotide and are represented by the formula 5' GCGX<sub>n</sub>GCG 3' in which X is a nucleotide and n is an integer between 0 and 50.

The nucleic acids used as either test or reference compounds can be double-stranded or single-stranded. They can be deoxyribonucleotide (DNA) or ribonucleotide (RNA) molecules. Generally, double-stranded molecules are more stable in vivo, while single-stranded molecules have increased immune activity. Thus in some the nucleic acid is single-stranded and in other embodiments the nucleic acid is double-stranded. In certain embodiments, while the nucleic acid is single-stranded, it is capable of forming secondary and tertiary structures (e.g., by folding back on itself, or by hybridizing with itself either throughout its entirety or at select segments along its length). Accordingly, while the primary structure of such a nucleic acid may be single-stranded, its higher order structures may be double- or triple-stranded.

For facilitating uptake into cells, the nucleic acids are preferably in the range of 6 to 100 bases in length. However, nucleic acids of any size equal to or greater than 6 nucleotides (even many kb long) are capable of inducing an immune response. Preferably the nucleic acid is in the range of between 8 and 100 and in some embodiments between 8 and 50 or 8 and 30 nucleotides in size.

The terms "nucleic acid" and "oligonucleotide" are used interchangeably to mean multiple nucleotides (i.e., molecules comprising a sugar (e.g., ribose or deoxyribose) linked to a phosphate group and to an exchangeable organic base, which is either a substituted pyrimidine (e.g., cytosine (C), thymine (T) or uracil (U)) or a substituted purine (e.g., adenine (A) or guanine (G)). As used herein, the terms "nucleic acid" and "oligonucleotide" refer to oligoribonucleotides as well as oligodeoxyribonucleotides. The terms "nucleic acid" and "oligonucleotide" shall also include polynucleosides (i.e., a polynucleotide minus the phosphate) and any other organic base containing polymer. Nucleic acid molecules can be obtained from existing nucleic acid sources (e.g., genomic or cDNA), but are preferably synthetic (e.g., produced by nucleic acid synthesis).

The terms "nucleic acid" and "oligonucleotide" also encompass nucleic acids or oligonucleotides with substitutions or modifications, such as in the bases and/or sugars. For example, they include nucleic acids having backbone sugars that are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 2' position and other than a phosphate group or hydroxy group at the 5' position. Thus modified nucleic acids may include a 2'-O-alkylated ribose group. In addition, modified nucleic acids may include sugars such as arabinose or 2'-fluoroarabinose instead of ribose. Thus the nucleic acids may be heterogeneous in backbone composition thereby containing any possible combination of polymer units linked together such as peptide-nucleic acids (which have an amino acid backbone with nucleic acid bases). Other examples are described in more detail below.

The immunostimulatory and immunoinhibitory nucleic acids can encompass various chemical modifications and substitutions, in comparison to natural RNA and DNA, involving a phosphodiester internucleoside bridge, a  $\beta$ -D-ribose unit and/or a natural nucleoside base (adenine, guanine, cytosine, thymine, uracil). Examples of chemical modifications are known to the skilled person and are described, for example, in Uhlmann E et al. (1990) *Chem Rev* 90:543; "Protocols for Oligonucleotides and Analogs" Synthesis and Properties & Synthesis and Analytical Techniques, S. Agrawal, Ed, Humana Press, Totowa, USA 1993; Crooke ST et al. (1996) *Annu Rev Pharmacol Toxicol* 36:107-129; and Hunziker J et al. (1995) *Mod Synth*

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*Methods* 7:331-417. An oligonucleotide according to the invention may have one or more modifications, wherein each modification is located at a particular phosphodiester internucleoside bridge and/or at a particular  $\beta$ -D-ribose unit and/or at a particular natural nucleoside base position in comparison to an oligonucleotide of the same sequence which is composed of natural DNA or RNA.

For example, the oligonucleotides may comprise one or more modifications and wherein each modification is independently selected from:

- a) the replacement of a phosphodiester internucleoside bridge located at the 3' and/or the 5' end of a nucleoside by a modified internucleoside bridge,
- 10 b) the replacement of phosphodiester bridge located at the 3' and/or the 5' end of a nucleoside by a dephospho bridge,
- c) the replacement of a sugar phosphate unit from the sugar phosphate backbone by another unit,
- d) the replacement of a  $\beta$ -D-ribose unit by a modified sugar unit, and
- 15 e) the replacement of a natural nucleoside base by a modified nucleoside base.

More detailed examples for the chemical modification of an oligonucleotide are as follows.

The oligonucleotides may include modified internucleotide linkages, such as those described in (a) or (b) above. These modified linkages may be partially resistant to degradation (e.g., are stabilized). A "stabilized oligonucleotide molecule" shall mean an oligonucleotide that is relatively resistant to *in vivo* degradation (e.g., via an exo- or endonuclease) resulting from such modifications. Oligonucleotides having phosphorothioate linkages, in some embodiments, may provide maximal activity and protect the oligonucleotide from degradation by intracellular exo- and endo-nucleases.

25 A phosphodiester internucleoside bridge located at the 3' and/or the 5' end of a nucleoside can be replaced by a modified internucleoside bridge, wherein the modified internucleoside bridge is for example selected from phosphorothioate, phosphorodithioate,  $\text{NR}^1\text{R}^2$ -phosphoramidate, boranophosphate,  $\alpha$ -hydroxybenzyl phosphonate, phosphate-( $\text{C}_1$ - $\text{C}_{21}$ )-O-alkyl ester, phosphate-[( $\text{C}_6$ - $\text{C}_{12}$ )aryl-( $\text{C}_1$ - $\text{C}_{21}$ )-O-alkyl]ester, ( $\text{C}_1$ - $\text{C}_8$ )alkylphosphonate  
 30 and/or ( $\text{C}_6$ - $\text{C}_{12}$ )arylphosphonate bridges, ( $\text{C}_7$ - $\text{C}_{12}$ )- $\alpha$ -hydroxymethyl-aryl (e.g., disclosed in WO 95/01363), wherein ( $\text{C}_6$ - $\text{C}_{12}$ )aryl, ( $\text{C}_6$ - $\text{C}_{20}$ )aryl and ( $\text{C}_6$ - $\text{C}_{14}$ )aryl are optionally substituted by halogen, alkyl, alkoxy, nitro, cyano, and where  $\text{R}^1$  and  $\text{R}^2$  are, independently of each other, hydrogen, ( $\text{C}_1$ - $\text{C}_{18}$ )-alkyl, ( $\text{C}_6$ - $\text{C}_{20}$ )-aryl, ( $\text{C}_6$ - $\text{C}_{14}$ )-aryl-( $\text{C}_1$ - $\text{C}_8$ )-alkyl, preferably hydrogen,

(C<sub>1</sub>-C<sub>8</sub>)-alkyl, preferably (C<sub>1</sub>-C<sub>4</sub>)-alkyl and/or methoxyethyl, or R<sup>1</sup> and R<sup>2</sup> form, together with the nitrogen atom carrying them, a 5-6-membered heterocyclic ring which can additionally contain a further heteroatom from the group O, S and N.

The replacement of a phosphodiester bridge located at the 3' and/or the 5' end of a nucleoside by a dephospho bridge (dephospho bridges are described, for example, in Uhlmann E and Peyman A in "Methods in Molecular Biology", Vol. 20, "Protocols for Oligonucleotides and Analogs", S. Agrawal, Ed., Humana Press, Totowa, 1993, Chapter 16, pp. 355 ff), wherein a dephospho bridge is for example selected from the dephospho bridges formacetal, 3'-thioformacetal, methylhydroxylamine, oxime, methylenedimethyl-hydrazo, dimethylenesulfone and/or silyl groups.

A sugar phosphate unit (i.e., a  $\beta$ -D-ribose and phosphodiester internucleoside bridge together forming a sugar phosphate unit) from the sugar phosphate backbone (i.e., a sugar phosphate backbone is composed of sugar phosphate units) can be replaced by another unit, wherein the other unit is for example suitable to build up a "morpholino-derivative" oligomer (as described, for example, in Stirchak EP et al. (1989) *Nucleic Acids Res* 17:6129-41), that is, e.g., the replacement by a morpholino-derivative unit; or to build up a polyamide nucleic acid ("PNA"; as described for example, in Nielsen PE et al. (1994) *Bioconjug Chem* 5:3-7), that is, e.g., the replacement by a PNA backbone unit, e.g., by 2-aminoethylglycine. The oligonucleotide may have other carbohydrate backbone modifications and replacements, such as peptide nucleic acids with phosphate groups (PHONA), locked nucleic acids (LNA), and oligonucleotides having backbone sections with alkyl linkers or amino linkers. The alkyl linker may be branched or unbranched, substituted or unsubstituted, and chirally pure or a racemic mixture.

A  $\beta$ -ribose unit or a  $\beta$ -D-2'-deoxyribose unit can be replaced by a modified sugar unit, wherein the modified sugar unit is for example selected from  $\beta$ -D-ribose,  $\alpha$ -D-2'-deoxyribose, L-2'-deoxyribose, 2'-F-2'-deoxyribose, 2'-F-arabinose, 2'-O-(C<sub>1</sub>-C<sub>6</sub>)alkyl-ribose, preferably 2'-O-(C<sub>1</sub>-C<sub>6</sub>)alkyl-ribose is 2'-O-methylribose, 2'-O-(C<sub>2</sub>-C<sub>6</sub>)alkenyl-ribose, 2'-[O-(C<sub>1</sub>-C<sub>6</sub>)alkyl-O-(C<sub>1</sub>-C<sub>6</sub>)alkyl]-ribose, 2'-NH<sub>2</sub>-2'-deoxyribose,  $\beta$ -D-xylo-furanose,  $\alpha$ -arabinofuranose, 2,4-dideoxy- $\beta$ -D-erythro-hexo-pyranose, and carbocyclic (described, for example, in Froehler J (1992) *Am Chem Soc* 114:8320) and/or open-chain sugar analogs (described, for example, in Vandendriessche et al. (1993) *Tetrahedron* 49:7223) and/or bicyclosugar analogs (described, for example, in Tarkov M et al. (1993) *Helv Chim Acta* 76:481).



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In some embodiments the sugar is 2'-O-methylribose, particularly for one or both nucleotides linked by a phosphodiester or phosphodiester-like internucleoside linkage.

In some embodiments, the nucleic acids may be soft or semi-soft nucleic acids. A soft nucleic acid is an immunostimulatory nucleic acid having a partially stabilized backbone, in which phosphodiester or phosphodiester-like internucleotide linkages occur only within and immediately adjacent to at least one internal pyrimidine -purine dinucleotide (YZ). Preferably YZ is YG, a pyrimidine-guanosine (YG) dinucleotide. The at least one internal YZ dinucleotide itself has a phosphodiester or phosphodiester-like internucleotide linkage. A phosphodiester or phosphodiester-like internucleotide linkage occurring immediately adjacent to the at least one internal YZ dinucleotide can be 5', 3', or both 5' and 3' to the at least one internal YZ dinucleotide.

In particular, phosphodiester or phosphodiester-like internucleotide linkages involve "internal dinucleotides". An internal dinucleotide in general shall mean any pair of adjacent nucleotides connected by an internucleotide linkage, in which neither nucleotide in the pair of nucleotides is a terminal nucleotide, i.e., neither nucleotide in the pair of nucleotides is a nucleotide defining the 5' or 3' end of the nucleic acid. Thus a linear nucleic acid that is n nucleotides long has a total of n-1 dinucleotides and only n-3 internal dinucleotides. Each internucleotide linkage in an internal dinucleotide is an internal internucleotide linkage. Thus a linear nucleic acid that is n nucleotides long has a total of n-1 internucleotide linkages and only n-3 internal internucleotide linkages. The strategically placed phosphodiester or phosphodiester-like internucleotide linkages, therefore, refer to phosphodiester or phosphodiester-like internucleotide linkages positioned between any pair of nucleotides in the nucleic acid sequence. In some embodiments the phosphodiester or phosphodiester-like internucleotide linkages are not positioned between either pair of nucleotides closest to the 5' or 3' end.

Preferably a phosphodiester or phosphodiester-like internucleotide linkage occurring immediately adjacent to the at least one internal YZ dinucleotide is itself an internal internucleotide linkage. Thus for a sequence  $N_1$  YZ  $N_2$ , wherein  $N_1$  and  $N_2$  are each, independent of the other, any single nucleotide, the YZ dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, and in addition (a)  $N_1$  and Y are linked by a phosphodiester or phosphodiester-like internucleotide linkage when  $N_1$  is an internal nucleotide, (b) Z and  $N_2$  are linked by a phosphodiester or phosphodiester-like internucleotide linkage when  $N_2$  is an internal nucleotide, or (c)  $N_1$  and Y are linked by a phosphodiester or

phosphodiester-like internucleotide linkage when  $N_1$  is an internal nucleotide and Z and  $N_2$  are linked by a phosphodiester or phosphodiester-like internucleotide linkage when  $N_2$  is an internal nucleotide.

Soft nucleic acids according to the instant invention are believed to be relatively  
5 susceptible to nuclease cleavage compared to completely stabilized nucleic acids. Without meaning to be bound to a particular theory or mechanism, it is believed that soft nucleic acids of the invention are cleavable to fragments with reduced or no immunostimulatory activity relative to full-length soft nucleic acids. Incorporation of at least one nuclease-sensitive internucleotide linkage, particularly near the middle of the nucleic acid, is believed to provide  
10 an "off switch" which alters the pharmacokinetics of the nucleic acid so as to reduce the duration of maximal immunostimulatory activity of the nucleic acid. This can be of particular value in tissues and in clinical applications in which it is desirable to avoid injury related to chronic local inflammation or immunostimulation, e.g., the kidney.

A semi-soft nucleic acid is an immunostimulatory nucleic acid having a partially  
15 stabilized backbone, in which phosphodiester or phosphodiester-like internucleotide linkages occur only within at least one internal pyrimidine-purine (YZ) dinucleotide. Semi-soft nucleic acids generally possess increased immunostimulatory potency relative to corresponding fully stabilized immunostimulatory nucleic acids. Due to the greater potency of semi-soft nucleic acids, semi-soft nucleic acids may be used, in some instances, at lower  
20 effective concentrations and have lower effective doses than conventional fully stabilized immunostimulatory nucleic acids in order to achieve a desired biological effect.

It is believed that the foregoing properties of semi-soft nucleic acids generally increase with increasing "dose" of phosphodiester or phosphodiester-like internucleotide linkages involving internal YZ dinucleotides. Thus it is believed, for example, that generally for a  
25 given nucleic acid sequence with five internal YZ dinucleotides, a nucleic acid with five internal phosphodiester or phosphodiester-like YZ internucleotide linkages is more immunostimulatory than a nucleic acid with four internal phosphodiester or phosphodiester-like YG internucleotide linkages, which in turn is more immunostimulatory than a nucleic acid with three internal phosphodiester or phosphodiester-like YZ internucleotide linkages,  
30 which in turn is more immunostimulatory than a nucleic acid with two internal phosphodiester or phosphodiester-like YZ internucleotide linkages, which in turn is more immunostimulatory than a nucleic acid with one internal phosphodiester or phosphodiester-like YZ internucleotide linkage. Importantly, inclusion of even one internal phosphodiester or

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phosphodiester-like YZ internucleotide linkage is believed to be advantageous over no internal phosphodiester or phosphodiester-like YZ internucleotide linkage. In addition to the number of phosphodiester or phosphodiester-like internucleotide linkages, the position along the length of the nucleic acid can also affect potency.

5           The soft and semi-soft nucleic acids will generally include, in addition to the phosphodiester or phosphodiester-like internucleotide linkages at preferred internal positions, 5' and 3' ends that are resistant to degradation. Such degradation-resistant ends can involve any suitable modification that results in an increased resistance against exonuclease digestion over corresponding unmodified ends. For instance, the 5' and 3' ends can be stabilized by the  
10           inclusion thereof at least one phosphate modification of the backbone. In a preferred embodiment, the at least one phosphate modification of the backbone at each end is independently a phosphorothioate, phosphorodithioate, methylphosphonate, or methylphosphorothioate internucleotide linkage. In another embodiment, the degradation-resistant end includes one or more nucleotide units connected by peptide or amide linkages at  
15           the 3' end.

          A phosphodiester internucleotide linkage is the type of linkage characteristic of nucleic acids found in nature. The phosphodiester internucleotide linkage includes a phosphorus atom flanked by two bridging oxygen atoms and bound also by two additional oxygen atoms, one charged and the other uncharged. Phosphodiester internucleotide linkage  
20           is particularly preferred when it is important to reduce the tissue half-life of the nucleic acid.

          A phosphodiester-like internucleotide linkage is a phosphorus-containing bridging group that is chemically and/or diastereomerically similar to phosphodiester. Measures of similarity to phosphodiester include susceptibility to nuclease digestion and ability to activate RNase H. Thus for example phosphodiester, but not phosphorothioate, nucleic acids are  
25           susceptible to nuclease digestion, while both phosphodiester and phosphorothioate nucleic acids activate RNase H. In a preferred embodiment the phosphodiester-like internucleotide linkage is boranophosphate (or equivalently, boranophosphonate) linkage. U.S. Patent No. 5,177,198; U.S. Patent No. 5,859,231; U.S. Patent No. 6,160,109; U.S. Patent No. 6,207,819; Sergueev et al., (1998) *J Am Chem Soc* 120:9417-27. In another preferred embodiment the  
30           phosphodiester-like internucleotide linkage is diastereomerically pure Rp phosphorothioate. It is believed that diastereomerically pure Rp phosphorothioate is more susceptible to nuclease digestion and is better at activating RNase H than mixed or diastereomerically pure Sp phosphorothioate. Stereoisomers of CpG nucleic acids are the subject of co-pending U.S.

patent application 09/361,575 filed July 27, 1999, and published PCT application PCT/US99/17100 (WO 00/06588). It is to be noted that for purposes of the instant invention, the term "phosphodiester-like internucleotide linkage" specifically excludes phosphorodithioate and methylphosphonate internucleotide linkages.

5       As described above the soft and semi-soft nucleic acids of the invention may have phosphodiester like linkages between C and G. One example of a phosphodiester-like linkage is a phosphorothioate linkage in an R<sub>p</sub> conformation. Nucleic acid p-chirality can have apparently opposite effects on the immune activity of a CpG nucleic acid, depending upon the time point at which activity is measured. At an early time point of 40 minutes, the R<sub>p</sub> but not  
10   the S<sub>p</sub> stereoisomer of phosphorothioate CpG nucleic acid induces JNK phosphorylation in mouse spleen cells. In contrast, when assayed at a late time point of 44 hr, the S<sub>p</sub> but not the R<sub>p</sub> stereoisomer is active in stimulating spleen cell proliferation. This difference in the kinetics and bioactivity of the R<sub>p</sub> and S<sub>p</sub> stereoisomers does not result from any difference in cell uptake, but rather most likely is due to two opposing biologic roles of the p-chirality.  
15   First, the enhanced activity of the R<sub>p</sub> stereoisomer compared to the S<sub>p</sub> for stimulating immune cells at early time points indicates that the R<sub>p</sub> may be more effective at interacting with the CpG receptor, TLR9, or inducing the downstream signaling pathways. On the other hand, the faster degradation of the R<sub>p</sub> PS-nucleic acids compared to the S<sub>p</sub> results in a much shorter duration of signaling, so that the S<sub>p</sub> PS-nucleic acids appear to be more biologically  
20   active when tested at later time points.

A surprisingly strong effect is achieved by the p-chirality at the CpG dinucleotide itself. In comparison to a stereo-random CpG nucleic acid the congener in which the single CpG dinucleotide was linked in R<sub>p</sub> was slightly more active, while the congener containing an S<sub>p</sub> linkage was nearly inactive for inducing spleen cell proliferation.

25       Nucleic acids also include substituted purines and pyrimidines such as C-5 propyne pyrimidine and 7-deaza-7-substituted purine modified bases. Wagner RW et al. (1996) *Nat Biotechnol* 14:840-4. Purines and pyrimidines include but are not limited to adenine, cytosine, guanine, and thymine, and other naturally and non-naturally occurring nucleobases, substituted and unsubstituted aromatic moieties.

30       A modified base is any base which is chemically distinct from the naturally occurring bases typically found in DNA and RNA such as T, C, G, A, and U, but which share basic chemical structures with these naturally occurring bases. The modified nucleoside base may be, for example, selected from hypoxanthine, uracil, dihydrouracil, pseudouracil, 2-thiouracil,

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4-thiouracil, 5-aminouracil, 5-(C<sub>1</sub>-C<sub>6</sub>)-alkyluracil, 5-(C<sub>2</sub>-C<sub>6</sub>)-alkenyluracil, 5-(C<sub>2</sub>-C<sub>6</sub>)-alkynyluracil, 5-(hydroxymethyl)uracil, 5-chlorouracil, 5-fluorouracil, 5-bromouracil, 5-hydroxycytosine, 5-(C<sub>1</sub>-C<sub>6</sub>)-alkylcytosine, 5-(C<sub>2</sub>-C<sub>6</sub>)-alkenylcytosine, 5-(C<sub>2</sub>-C<sub>6</sub>)-alkynylcytosine, 5-chlorocytosine, 5-fluorocytosine, 5-bromocytosine, N<sup>2</sup>-dimethylguanine, 5 2,4-diamino-purine, 8-azapurine, a substituted 7-deazapurine, preferably 7-deaza-7-substituted and/or 7-deaza-8-substituted purine, 5-hydroxymethylcytosine, N4-alkylcytosine, e.g., N4-ethylcytosine, 5-hydroxydeoxycytidine, 5-hydroxymethyldeoxycytidine, N4-alkyldeoxycytidine, e.g., N4-ethyldeoxycytidine, 6-thiodeoxyguanosine, and deoxyribonucleosides of nitropyrrole, C5-propynylpyrimidine, and 10 diaminopurine e.g., 2,6-diaminopurine, inosine, 5-methylcytosine, 2-aminopurine, 2-amino-6-chloropurine, hypoxanthine or other modifications of a natural nucleoside bases. This list is meant to be exemplary and is not to be interpreted to be limiting.

Modified cytosines include but are not limited to 5-substituted cytosines (e.g., 5-methyl-cytosine, 5-fluoro-cytosine, 5-chloro-cytosine, 5-bromo-cytosine, 5-iodo-cytosine, 5- 15 hydroxy-cytosine, 5-hydroxymethyl-cytosine, 5-difluoromethyl-cytosine, and unsubstituted or substituted 5-alkynyl-cytosine), 6-substituted cytosines, N4-substituted cytosines (e.g., N4-ethyl-cytosine), 5-aza-cytosine, 2-mercapto-cytosine, isocytosine, pseudo-isocytosine, cytosine analogs with condensed ring systems (e.g., N,N'-propylene cytosine or phenoxazine), and uracil and its derivatives (e.g., 5-fluoro-uracil, 5-bromo-uracil, 5-bromovinyl-uracil, 4-thio-uracil, 5-hydroxy-uracil, 5-propynyl-uracil). In another 20 embodiment, the cytosine base is substituted by a universal base (e.g., 3-nitropyrrole, P-base), an aromatic ring system (e.g., fluorobenzene or difluorobenzene) or a hydrogen atom (dSpacer).

Modified guanines include but are not limited to 7-deazaguanine, 25 7-deaza-7-substituted guanine (such as 7-deaza-7-(C<sub>2</sub>-C<sub>6</sub>)alkynylguanine), 7-deaza-8-substituted guanine, hypoxanthine, N2-substituted guanines (e.g., N2-methyl-guanine), 5-amino-3-methyl-3H,6H-thiazolo[4,5-d]pyrimidine-2,7-dione, 2,6-diaminopurine, 2-aminopurine, purine, indole, adenine, substituted adenines (e.g., N6-methyl-adenine, 8-oxo-adenine) 8-substituted guanine (e.g., 8-hydroxyguanine and 8-bromoguanine), and 30 6-thioguanine. In another embodiment, the guanine base is substituted by a universal base (e.g., 4-methyl-indole, 5-nitro-indole, and K-base), an aromatic ring system (e.g., benzimidazole or dichloro-benzimidazole, 1-methyl-1H-[1,2,4]triazole-3-carboxylic acid amide) or a hydrogen atom (dSpacer).

For use in the instant invention, the oligonucleotide reference compounds and test compounds can be synthesized *de novo* using any of a number of procedures well known in the art, for example, the  $\beta$ -cyanoethyl phosphoramidite method (Beaucage SL et al. (1981) *Tetrahedron Lett* 22:1859), or the nucleoside H-phosphonate method (Garegg et al. (1986) *Tetrahedron Lett* 27:4051-4; Froehler BC et al. (1986) *Nucleic Acids Res* 14:5399-407; Garegg et al (1986) *Tetrahedron Lett* 27:4055-8; Gaffney et al. (1988) *Tetrahedron Lett* 29:2619-22). These chemistries can be performed by a variety of automated nucleic acid synthesizers available in the market. These oligonucleotides are referred to as synthetic oligonucleotides. An isolated oligonucleotide generally refers to an oligonucleotide which is separated from components which it is normally associated with in nature. As an example, an isolated oligonucleotide may be one which is separated from a cell, from a nucleus, from mitochondria or from chromatin.

Modified backbones such as phosphorothioates can be synthesized using automated techniques employing either phosphoramidate or H-phosphonate chemistries. Aryl- and alkyl-phosphonates can be made, e.g., as described in U.S. Pat. No. 4,469,863; and alkylphosphotriesters (in which the charged oxygen moiety is alkylated as described in U.S. Pat. No. 5,023,243 and European Pat. No. 092,574) can be prepared by automated solid phase synthesis using commercially available reagents. Methods for making other DNA backbone modifications and substitutions have been described (e.g., Uhlmann E et al. (1990) *Chem Rev* 90:544; Goodchild J (1990) *Bioconjugate Chem* 1:165).

#### TLR expression

The cell lines can be used in their native state without any modification. For example, in the case of the RPMI 8226 cell line, it can be used to identify compounds that signal through at least TLR9 and/or TLR7. In other instances, however, the cell line can be modified to express a TLR that it does not naturally express. In still other instances, the cell to be used in the screening method may express one or more endogenous TLR and yet still be manipulated to express an additional TLR different from those it endogenously expresses. The cell may also be manipulated in order to increase or decrease the level of TLR that it endogenously expresses. The cells may be stably or transiently transfected.

A cell that does not naturally express a protein or polypeptide, but is genetically manipulated to do so is referred to as ectopically expressing the protein or polypeptide.

The basic screening method remains the same regardless of which TLR is expressed by the cell. However, the reference compound and the readout may vary depending upon the TLR(s) expressed. In the most simple aspect, the screening method is used to identify a compound that signals through a TLR such as for example TLR9. In this case, the positive  
5 reference compound may be an immunostimulatory compound already known to act through TLR9 (e.g., CpG nucleic acid).

The methods of the invention involve, in part, contacting a functional TLR with a test composition. A functional TLR is a full-length TLR protein or a fragment thereof capable of inducing or inhibiting a signal in response to interaction with its ligand. Generally the  
10 functional TLR will include at least a TLR ligand-binding fragment of the extracellular domain of the full-length TLR and at least a fragment of a TIR domain capable of interacting with another Toll homology domain-containing polypeptide, e.g., MyD88. In various embodiments the functional TLR is a full-length TLR selected from TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, and TLR10.

To date, there are eleven TLRs known. Nucleic acid and amino acid sequences for ten  
15 currently known human TLRs are available from public databases such as GenBank. Similarly, nucleic acid and amino acid sequences for various TLRs from numerous non-human species are also available from public databases including GenBank. For example, nucleic acid and amino acid sequences for human TLR9 (hTLR9) can be found as GenBank  
20 accession numbers AF245704 (coding region spanning nucleotides 145-3243) (SEQ ID NO: 60) and AAF78037 (SEQ ID NO: 62), respectively. Nucleic acid and amino acid sequences for murine TLR9 (mTLR9) can be found as GenBank accession numbers AF348140 (coding region spanning nucleotides 40-3138) (SEQ ID NO: 68) and AAK29625 (SEQ ID NO: 72), respectively.

Nucleic acid and amino acid sequences for human TLR8 (hTLR8) can be found as  
25 GenBank accession numbers AF245703 (coding region spanning nucleotides 49-3174) (SEQ ID NO: 46) and AAF78036 (SEQ ID NO: 50), respectively. Nucleic acid and amino acid sequences for murine TLR8 (mTLR8) can be found as GenBank accession numbers AY035890 (coding region spanning nucleotides 59-3157) (SEQ ID NO: 55) and AAK62677  
30 (SEQ ID NO: 57), respectively.

Nucleic acid and amino acid sequences for human TLR7 (hTLR7) can be found as GenBank accession numbers AF240467 (coding region spanning nucleotides 135-3285) (SEQ ID NO: 31) and AAF60188 (SEQ ID NO: 34), respectively. Nucleic acid and amino acid

sequences for murine TLR7 (mTLR7) can be found as GenBank accession numbers AY035889 (coding region spanning nucleotides 49-3201) (SEQ ID NO: 38) and AAK62676 (SEQ ID NO: 41), respectively.

Nucleic acid and amino acid sequences for human TLR3 (hTLR3) can be found as GenBank accession numbers NM\_003265 (coding region spanning nucleotides 102-2816) (SEQ ID NO: 7) and NP\_003256 (SEQ ID NO: 8), respectively. Nucleic acid and amino acid sequences for murine TLR3 (hTLR3) can be found as GenBank accession numbers AF355152 (coding region spanning nucleotides 44-2761) (SEQ ID NO: 9) and AAK26117 (SEQ ID NO: 10), respectively.

Nucleic acid and amino acid sequences for human TLR1 (hTLR1) can be found as GenBank accession numbers NM\_003263 and NP\_003254, respectively. Nucleic acid and amino acid sequences for murine TLR1 (mTLR1) can be found as GenBank accession numbers NM\_030682 and NP\_109607, respectively.

The functional TLR also is not limited to native TLR polypeptides. As used herein, a native TLR is one that is naturally occurring. The TLR may be a non-native (or non-naturally occurring TLR). An example is a chimeric TLR having an extracellular domain and the cytoplasmic domain derived from TLRs from different species. Such chimeric TLR polypeptides can include, for example, a human TLR extracellular domain and a murine TLR cytoplasmic domain. In alternative embodiments, such chimeric TLR polypeptides can include chimerae created with different TLR splice variants or allotypes.

#### TLR Signaling Pathways

The screening methods provided by the invention measure TLR signaling activity.

TLR signaling activity is activity that results from interaction of a TLR with a TLR ligand.

TLR signaling can be measured in a number of ways including but not limited to interaction between a TLR and a protein or factor (such as an adaptor protein), interaction between downstream proteins or factors (such as an adaptor protein) with each other, activation of nuclear factors such as transcription factors or transcription complexes, up- or down-regulation of genes, phosphorylation or dephosphorylation of proteins or factors in the signaling cascade, expression, production and/or secretion of cytokines and/or chemokines, changes in cell cycle status, up- or down-regulation of cell surface marker expression, and the like. Those of ordinary skill in the art are familiar with assays for measuring these latter



events including but not limited to gel shift assays, immunoprecipitations, phosphorylation status analysis of proteins, Northern analysis, RT-PCR analysis, etc.

The following is an exemplary TLR signaling pathway or cascade. It is to be understood that this is meant to be illustrative and that different factors may be involved in the signaling of particular TLR. One TLR signaling pathway is known to use the cytoplasmic Toll/IL-1 receptor (TIR) homology domain, present in all TLRs. This domain interacts (e.g., binds to) and thereby transduces a signal to a similar domain on an adapter protein (e.g., MyD88). This type of interaction is referred to as a like:like interaction of TIR domains. This interaction is followed by an another interaction between the adapter protein and a kinase, through their respective "death domains". In the case of at least TLR4 signaling, the kinase then interacts with tumor necrosis factor (TNF) receptor-associated factor-6 (TRAF6). Medzhitov R et al., *Mol Cell* 2:253 (1998); Kopp EB et al., *Curr Opin Immunol* 11:15 (1999). After TRAF6, two sequential kinase activation steps lead to phosphorylation of the inhibitory protein I kappa B and its dissociation from NF- $\kappa$ B. The first kinase is a mitogen-activated kinase kinase kinase (MAPKKK) known as NIK, for NF- $\kappa$ B-inducing kinase. The target of this kinase is another kinase made up of two chains, called I kappa B kinase  $\alpha$  (IKK  $\alpha$ ) and I kappa B kinase  $\beta$  (IKK  $\beta$ ), that together form a heterodimer of IKK $\alpha$ :IKK $\beta$ , which phosphorylates I kappa B. NF- $\kappa$ B translocates to the nucleus to activate genes with kappa B binding sites in their promoters and enhancers such as the genes encoding IL-6, IL-8, the p40 subunit of IL-12, and the costimulatory molecule CD86. The signaling mechanisms of TLRs are not limited to this pathway; other signaling pathways exist and can be used in the screening readouts of the methods provided herein.

The screening assays employ a number of readouts (or parameters). The readouts can be native readouts. A native readout is one that does not rely on introduction of a reporter construct into the cell of interest. The readouts can be artificial. An artificial readout is one that relies on introduction of a reporter construct into the cell of interest. Examples of both are provided herein. In still other embodiments, a given assay may measure one or more native readouts and one or more artificial readouts. Each readout whether native or artificial is related to signaling pathways that ensue after TLR engagement with a ligand.

Each cell line described herein will be associated with a particular set of native readouts which the invention seeks to determine in the screening assays provided. As an example, the response of the RPMI 8226 cell line to an immunomodulatory molecule can be assessed in terms of native readouts such as CD71 expression, CD86 expression, HLA-DR

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expression, IL-8 expression, IL-8 production, IL-8 secretion, IL-10 expression, IL-10 production, IL-10 secretion, IP-10 expression, IP-10 production, IP-10 secretion, TNF- $\alpha$  expression, TNF- $\alpha$  production and TNF- $\alpha$  secretion. RAMOS response can be assessed, inter alia, by CD80 cell surface expression. Raji response can be assessed, inter alia, by IL-6 secretion.

As described in greater detail herein, the cell line can be used in an unmodified form. In one respect, an unmodified cell line will naturally respond to a TLR ligand through a native readout system. For example, an RPMI 8226 cell exposed to an immunostimulatory TLR ligand may increase expression of IP-10 from the native gene locus. Alternatively, the cell line may be modified to contain a reporter construct that acts as a surrogate for the IP-10 gene locus. For example, the reporter construct may contain the TLR responsive promoter elements that are naturally found in the native IP-10 locus operably linked to a reporter coding sequence that encodes a gene product that is detectable and quantifiable. The structure and variability of suitable reporter constructs will be discussed in greater detail herein.

Readouts typically include the induction of a gene under control of a specific promoter such as a NF- $\kappa$ B promoter. The gene under the control of the NF- $\kappa$ B promoter can be a gene which naturally includes an NF- $\kappa$ B promoter or it can be a gene in a construct in which an NF- $\kappa$ B promoter has been inserted. Endogenous genes and transfected constructs which include the NF- $\kappa$ B promoter include but are not limited to IL-8, IL-12 p40, NF- $\kappa$ B-luc, IL-12 p40-luc, and TNF-luc.

Increases in cytokine levels can result from increased production, increased stability, increased secretion, or any combination of the foregoing, of the cytokine in response to the TLR-mediated signaling. Cytokines generally include, without limitation, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-11, IL-12, IL-13, IL-15, IL-18, IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , TNF- $\alpha$ , GM-CSF, G-CSF, M-CSF. Th1 cytokines include but are not limited to IL-2, IFN- $\gamma$ , and IL-12. Th2 cytokines include but are not limited to IL-4, IL-5, and IL-10.

Increases in chemokine levels can result from increased production, increased stability, increased secretion, or any combination of the foregoing, of the chemokine in response to the TLR-mediated signaling. Chemokines of particular significance in the invention include but are not limited to CCL5 (RANTES), CXCL9 (Mig), CXCL10 (IP-10), CXCL11 (I-TAC), IL-8, and MCP-1.

TLR signaling activity can also be measured by phosphorylation, such as total cellular phosphorylation or phosphorylation of specific factors such as but not limited to IRAK, ERK, MyD88, TRAF6, p38, NF- $\kappa$ B subunits, c-Jun and c-Fos.

5 TLR signaling activity can be measured by changes in gene expression. The expression of CD71, CD86, CD80, CD69, CD54, HLA-DR, HLA class I, IL-6, IL-8, IL-10, IP-9, IP-10, IFN- $\alpha$ , TNF- $\alpha$ , and the like can be assessed as a measure of TLR signaling activity. Gene expression analysis may be performed using microarray techniques.

TLR signaling activity can also be measured by cell proliferation status or changes thereto.

10 TLR signaling activity can also be measured by cell surface marker expression such as the cell surface expression of markers such as but not limited to CD71, CD86, HLA-DR, CD80, HLA class I, CD54 and CD69.

TLR signaling activity can also be measured by antibody secretion such as but not limited to IgM secretion.

15

#### Reporter and Expression Constructs

The cells can be manipulated by the introduction of expression and/or reporter constructs. The expression constructs preferably comprise a TLR coding sequence, as described above. The reporter constructs can be used as surrogate measures of native TLR  
20 signaling activity. These reporter constructs are intended to substitute for the "native" readouts capable with the cell line. In order to act as substitutes, the reporter constructs include a promoter element derived from a gene known to be modulated following TLR engagement with a TLR ligand. The reporter construct further includes a coding sequence linked to the promoter. The coding sequence is usually that of a reporter (i.e., a protein that is  
25 detectable or quantifiable).

The reporter construct generally includes a promoter, a coding sequence and a polyadenylation signal. These nucleic acids shall include, as necessary, 5' non-transcribing and 5' non-translating sequences involved with the initiation of transcription and translation, respectively, such as a TATA box, capping sequence, CAAT sequence, in addition to  
30 promoter elements that are responsive to TLR signaling. The nucleic acid constructs may optionally include enhancer sequences or upstream activator sequences as desired.

The promoter in the reporter construct will include a TLR responsive promoter element, and will therefore be regarded as a TLR responsive promoter. As used herein, a

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TLR responsive promoter is a promoter having an activity that is modulated (i.e., either activated or inhibited) by signaling through a TLR (e.g., by TLR interaction with its ligand). In order to be modulated by TLR signaling, the promoter contains sites that are bound by transcription factors modulated by TLR signaling. The factors may be activated or inhibited by TLR signaling. Activation of the transcription factor includes increases in the activity of the transcription factor per se, increases in its ability to interact with other factors or with DNA that serve to increase its activity, and increases in its transcription and translation (i.e., increased mRNA and protein levels of the transcription factor). Conversely, inhibition of the transcription factor includes decreases in the activity of the transcription factor per se, decreases in its ability to interact with other factors or with DNA that serve to decrease its activity, and decreases in its transcription and translation (i.e., decreased mRNA and protein levels of the transcription factor). The effect on the transcription factor is usually the downstream result of other interactions in the signaling pathway. The expression of coding sequences linked to such promoters will therefore be modulated by TLR signaling events, and it is the level of expression of these coding sequences that can be used as a readout of TLR signaling in the screening methods provided herein.

The TLR responsive promoter may comprise a transcription factor binding site selected from the group consisting of a NF- $\kappa$ B binding site, an AP-1 binding site, a CRE, a SRE, an interferon-stimulated response element (ISRE), a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE, among others. These binding sites and their sequences are known in the art. Below is an exemplary list of these sequences.

W = A or T, R = A or G, Y = C or T

NF- $\kappa$ B Binding site:

Consensus p50 subunit  
5' GGGGATYCCC 3' (SEQ ID NO:90)

Consensus p65 subunit  
5' GGGRNTTTC 3' (SEQ ID NO:91)

Example of p65 subunit binding site  
5' AGT TGA GGG GAC TTT CCC AGG C 3' (SEQ ID NO:92)

35

CREB Binding site:

5'AGA GAT TGC CTG ACG TCA GAG AGC TAG 3' (SEQ ID NO:93)

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## AP-1 Binding site:

5'- CGC TTG ATG AGT CAG CCG GAA -3' (SEQ ID NO:94)

5'- CGC ATG AGT CAG ACA -3' (SEQ ID NO:95)

## 5 ISRE :

5'- TGCAGAAGTGAAACTGAGG-3' (SEQ ID NO:96)

5'- AGAACGAAACA-3' (SEQ ID NO:97)

5'- GAGAAGTGAAAGTGG-3' (SEQ ID NO:98)

5'- TAAGAACATGAAACTGAA-3' (SEQ ID NO:99)

10 5'- ATGAAACTGAAAGTA-3' (SEQ ID NO:100)

5'- TGAAAACCGAAAGCGC-3' (SEQ ID NO:101)

5'- AGAAATGGAAAGT-3' (SEQ ID NO:102)

## SRE

15 5'- TCACCCAC-3' (SEQ ID NO:103)

5'- CTCACCCAC-3' (SEQ ID NO:104)

5'- GCCACCCTAC-3' (SEQ ID NO:105)

## NFAT:

20 5'- TATGAAACAGTTTTTCC -3' (SEQ ID NO:106)

5'- AGGAAACTC -3' (SEQ ID NO:107)

5'- ARGARATTCC -3' (SEQ ID NO:108)

5'- CCAGTTGAGCCAGAGA -3' (SEQ ID NO:109)

## 25 GAS:

5'- CTTTCAGTTTCATATTACTCTAAATCCATT -3' (SEQ ID NO:110)

## p53 Binding Site :

## 30 p53 Consensus site:

5'- RRCWWGYYY -3' (SEQ ID NO:111)

## Examples of p53 binding sites:

35 5'- AGGCATGCCT -3' (SEQ ID NO:112)

5'- GGGCTTGCCC -3' (SEQ ID NO:113)

5'- GGGCTTGCTT -3' (SEQ ID NO:114)

5'- GCCTGGACTTGCC -3' (SEQ ID NO:115)

5'- GGACATGCCCGGGCATGTCC -3' (SEQ ID NO:116)

5'- GTAGCATTAGCCCAGACATGTCC -3' (SEQ ID NO:117)

## 40

TARE (TNF- $\alpha$  response element):

e.g. from the COL1A1 promoter

5'GAGGTATGCAGACAAGAGTCAGAGTTTCCCCTTGAA 3' (SEQ ID NO:118)

## 45

## SRF

5'- CCWWWWWWGG -3' (SEQ ID NO:119)

5'- CCAAATAAGGC -3' (SEQ ID NO:120)

The TLR responsive promoter element can be derived from the promoter of a naturally occurring (i.e., an endogenous) gene that is activated or inhibited by TLR signaling (such as the IL-6 gene, the IL-8 gene, the IL-10 gene, the IL-12 p40 gene, the IP-9 gene, the IP-10 gene, the type 1 IFN gene, the IFN- $\alpha$ 4 gene, the IFN- $\beta$  gene, the TNF- $\alpha$  gene, the TNF- $\beta$  gene, the RANTES gene, the ITAC gene, the IGFBP4 gene, the CD54 gene, the CD69 gene, the CD71 gene, the CD80 gene, the CD86 gene, the HLA-DR gene, the HLA class I gene, and the like). The afore-mentioned genes are genes that are known to be activated in response to TLR interaction with its ligand.

Suitable promoter regions are described in the Examples. Briefly, the upstream (5') -620 to +50 promoter region of IFN- $\alpha$ 4 or the upstream (5') -140 to +9 promoter region of IFN- $\alpha$ 1 can be used. In one embodiment, the IFN- $\alpha$ 4 sequence is cloned into the *Sma*I site of the pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') promoter region of IFN- $\alpha$ 4.

The promoter can also be the upstream (5') -280 to +20 promoter region of IFN- $\beta$ .  
The promoter can also be the upstream (5') -397 to +5 promoter region of RANTES. In one embodiment, the RANTES promoter sequence is cloned into the *Nhe*I site (filled in with Klenow) of the pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') -397 to +5 promoter region of RANTES.

The promoter can also be the upstream truncated (-250 to +30) and full length (-860 to +30) promoter regions derived from human IL-12 p40 genomic DNA. In one embodiment, the truncated IL-12 p40 promoter was cloned as a *Kpn*I-*Xho*I insert into p $\beta$ gal-Basic (Promega) resulting in an expression vector that includes a  $\beta$  gal gene under the control of the upstream (5') -250 to +30 promoter region of human IL-12 p40. In another embodiment, the full length IL-12 p40 promoter was cloned as a *Kpn*I-*Xho*I insert into p $\beta$ gal-Basic (Promega) resulting in an expression vector that includes a  $\beta$  gal gene under the control of the upstream (5') -751 to +30 promoter region of human IL-12 p40. In another embodiment, the truncated -250 to +30 promoter region of human IL-12 p40 was cloned into the pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') -250 to +30 promoter region of human IL-12 p40. In yet another embodiment, the full length IL-12 p40 promoter of human IL-12 p40 was cloned into the

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pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') -751 to +30 promoter region of human IL-12 p40.

The promoter can also be the upstream (5') -288 to +7 promoter region derived from human IL-6 genomic DNA. The promoter can also be derived from the full-length promoter  
5 region of the IL-6 gene from -1174 to +7 (Accession No M22111, SEQ ID NO:129).

The promoter can also be the upstream (5') -734 to +44 or the upstream (5') -162 to +44 promoter region derived from human IL-8 genomic DNA. Mukaida N et al. (1989) *J Immunol* 143:1366-71.

The promoter can also be derived from the -615 to +30 promoter region of human  
10 TNF- $\alpha$ .

The promoter can also be derived from a promoter region of human TNF- $\beta$ .

The promoter can also be derived from the -875 to +97 promoter region of human IP-  
10.

The promoter can also be derived from the -219 to +114 promoter region of human  
15 CXCL11 (IP9). The promoter can also be derived from the full length (-934 to +114) promoter region of human CXCL11 (IP9).

The promoter can also be derived from the -289 to +217 promoter region of human IGFBP4 (Insulin growth factor binding protein 4). The promoter can also be derived from the full length (-836 to +217) promoter region of human IGFBP4.

The promoter response element generally will be present in multiple copies, e.g., as  
20 tandem repeats. For example, in one reporter construct, coding sequence for luciferase is under control of an upstream 6X tandem repeat of NF- $\kappa$ B response element. In another example, an ISRE-luciferase reporter construct useful in the invention is available from Stratagene (catalog no. 219092) and includes a 5x ISRE tandem repeat joined to a TATA box  
25 upstream of a luciferase reporter gene.

The reporter construct coding sequence is preferably any nucleotide sequence that codes for a protein capable of detection or quantification. The protein can be an enzyme (e.g., luciferase, alkaline phosphatase,  $\beta$ -galactosidase, chloramphenicol acetyltransferase (CAT), secreted alkaline phosphatase, etc.), a bioluminescence marker (e.g., green fluorescent protein  
30 (GFP, U.S. Pat. No. 5,491,084), etc.), blue fluorescent protein (BFP, e.g., U.S. Pat. No. 6,486,382), etc.), a surface-expressed molecule (e.g., CD25, CD80, CD86), a secreted molecule (e.g., IL-1, IL-6, IL-8, IL-12 p40, TNF- $\alpha$ ), a hapten or antigen, and other detectable protein products known to those of skill in the art. For assays relying on enzyme activity

readout, substrate can be supplied as part of the assay, and detection can involve measurement of chemiluminescence, fluorescence, color development, incorporation of radioactive label, drug resistance, or other marker of enzyme activity. For assays relying on surface expression of a molecule, detection can be accomplished using flow cytometry (FACS) analysis or  
5 functional assays. Secreted molecules can be assayed using enzyme-linked immunosorbent assay (ELISA) or bioassays. Many of these and other suitable readout systems are well known in the art and are commercially available. Preferably, the coding sequence encodes a protein having a level or an activity that is quantifiable, preferably with a wide linear range.

The expression construct coding sequence is preferably a TLR coding sequence  
10 derived from the sequences listed herein. Preferably, the expression construct promoter is a constitutive promoter, although in some embodiments it may be inducible. Those of ordinary skill in the art are familiar with such promoters.

As used herein, a coding sequence and the regulatory sequences (such as promoters) are said to be operably linked when they are covalently linked in such a way as to place the  
15 expression or transcription and/or translation of the coding sequence under the influence or control of the regulatory sequence. Two DNA sequences are said to be operably linked if induction of a promoter in the 5' regulatory sequence results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter  
20 region to direct the transcription of the coding sequence, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a regulatory sequence would be operably linked to a coding sequence if the gene expression sequence were capable of effecting transcription of that coding sequence such that the resulting transcript is translated into the desired protein or polypeptide.

25 Methods for nucleic acid introduction into cells are known in the art.

The nucleic acid may be delivered to the cells alone or in association with a vector. In its broadest sense, a vector is any vehicle capable of facilitating the transfer of the nucleic acid to the cells so that the reporter can be expressed. The vector generally transports the nucleic acid to the cells with reduced degradation relative to the extent of degradation that would  
30 result in the absence of the vector. In general, the vectors useful in the invention include, but are not limited to, plasmids, phagemids, viruses, other vehicles derived from viral or bacterial sources that have been manipulated by the insertion or incorporation of the antigen nucleic acid sequences. Viral vectors are a preferred type of vector and include, but are not limited



to, nucleic acid sequences from the following viruses: retrovirus, such as Moloney murine leukemia virus, Harvey murine sarcoma virus, murine mammary tumor virus, and Rous sarcoma virus; adenovirus, adeno-associated virus; SV40-type viruses; polyoma viruses; Epstein-Barr viruses; papilloma viruses; herpes virus; vaccinia virus; polio virus; and RNA virus such as a retrovirus. One can readily employ other vectors not named but known in the art.

Preferred viral vectors are based on non-cytopathic eukaryotic viruses in which non-essential genes have been replaced with the gene of interest. Non-cytopathic viruses include retroviruses, the life cycle of which involves reverse transcription of genomic viral RNA into DNA with subsequent proviral integration into host cellular DNA. Retroviruses have been approved for human gene therapy trials. Most useful are those retroviruses that are replication-deficient (i.e., capable of directing synthesis of the desired proteins, but incapable of manufacturing an infectious particle). Such genetically altered retroviral expression vectors have general utility for the high-efficiency transduction of genes *in vivo*. Standard protocols for producing replication-deficient retroviruses (including the steps of incorporation of exogenous genetic material into a plasmid, transfection of a packaging cell lined with plasmid, production of recombinant retroviruses by the packaging cell line, collection of viral particles from tissue culture media, and infection of the target cells with viral particles) are provided in Kriegler, M., Gene Transfer and Expression, A Laboratory Manual W.H. Freeman C.O., New York (1990) and Murray, E.J. Methods in Molecular Biology, vol. 7, Humana Press, Inc., Clifton, New Jersey (1991).

A preferred virus for certain applications is the adeno-associated virus, a double-stranded DNA virus. The adeno-associated virus can be engineered to be replication-deficient and is capable of infecting a wide range of cell types and species. It further has advantages such as, heat and lipid solvent stability; high transduction frequencies in cells of diverse lineages, including hemopoietic cells; and lack of superinfection inhibition thus allowing multiple series of transductions. Reportedly, wild-type adeno-associated virus manifest some preference for integration sites into human cellular DNA, thereby minimizing the possibility of insertional mutagenesis and variability of inserted gene expression characteristic of retroviral infection. In addition, wild-type adeno-associated virus infections have been followed in tissue culture for greater than 100 passages in the absence of selective pressure, implying that the adeno-associated virus genomic integration is a relatively stable event. The adeno-associated virus can also function in an extrachromosomal fashion.

Recombinant adeno-associated viruses that lack the replicase protein apparently lack this integration sequence specificity.

Other vectors include plasmid vectors. Plasmid vectors have been extensively described in the art and are well-known to those of skill in the art. See e.g., Sambrook et al.,  
5 Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989. In the last few years, plasmid vectors have been found to be particularly advantageous for delivering genes to cells *in vivo* because of their inability to replicate within and integrate into a host genome. These plasmids, however, having a promoter compatible with the host cell, can express a peptide from a gene operatively encoded within the plasmid.  
10 Some commonly used plasmids include pBR322, pUC18, pUC19, pRc/CMV, SV40, and pBlueScript. Other plasmids are well-known to those of ordinary skill in the art. Additionally, plasmids may be custom designed using restriction enzymes and ligation reactions to remove and add specific fragments of DNA.

In general, the vectors useful in the invention are divided into two classes: biological  
15 vectors and chemical/physical vectors. Biological vectors and chemical/physical vectors are useful in the delivery and/or uptake of reporter constructs of the invention.

Most biological vectors are used for delivery of nucleic acids and thus would be most appropriate in the delivery of nucleic acids.

As used herein, a "chemical/physical vector" refers to a natural or synthetic molecule,  
20 other than those derived from bacteriological or viral sources, capable of delivering the reference and test compound.

A preferred chemical/physical vector of the invention is a colloidal dispersion system. Colloidal dispersion systems include lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system of the invention is a  
25 liposome. Liposomes are artificial membrane vessels which are useful as a delivery vector *in vivo* or *in vitro*. It has been shown that large unilamellar vessels (LUV), which range in size from 0.2 - 4.0  $\mu\text{m}$  can encapsulate large macromolecules. RNA, DNA and intact virions can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, et al., *Trends Biochem. Sci.*, (1981) 6:77).

30 Liposomes may be targeted to a particular tissue by coupling the liposome to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein. Ligands which may be useful for targeting a liposome to an immune cell include, but are not limited to, intact or fragments of molecules which interact with immune cell specific receptors and molecules,

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such as antibodies, which interact with the cell surface markers of immune cells. Such ligands may easily be identified by binding assays well known to those of skill in the art. In still other embodiments, the liposome may be targeted to the cancer by coupling it to a one of the immunotherapeutic antibodies discussed earlier. Additionally, the vector may be coupled  
5 to a nuclear targeting peptide, which will direct the vector to the nucleus of the host cell.

Lipid formulations for transfection are commercially available from QIAGEN, for example, as EFFECTENE™ (a non-liposomal lipid with a special DNA condensing enhancer) and SUPERFECT™ (a novel acting dendrimeric technology).

Liposomes are commercially available from Gibco BRL, for example, as  
10 LIPOFECTIN™ and LIPOFECTACE™, which are formed of cationic lipids such as N-[1-(2, 3 dioleyloxy)-propyl]-N, N, N-trimethylammonium chloride (DOTMA) and dimethyl dioctadecylammonium bromide (DDAB). Methods for making liposomes are well known in the art and have been described in many publications. Liposomes also have been reviewed by Gregoriadis, G. in *Trends in Biotechnology*, (1985) 3:235-241. In some preferred  
15 embodiments, the method of choice for delivering DNA (for transfection) to the cells is electroporation, particularly where a stably transfected cell line is sought.

The present invention is further illustrated by the following Examples, which in no way should be construed as further limiting.

20

### Examples

#### **Example 1. Biological Activity of Production Lot of CpG ODN (SEQ ID NO:1) Assayed Using Cells Stably Transfected with hTLR9 Expression Vector**

CpG ODN (SEQ ID NO:1) is currently in preclinical and clinical trials for a number of  
25 clinical applications. SEQ ID NO:1 has been discovered to induce signaling through TLR9. In order to assess different lots of clinical material, the methods of the invention are employed, using a highly characterized lot of SEQ ID NO:1 as a reference.

In a TLR9 assay, the CpG-non-responsive human embryonal kidney cell line HEK293 (e.g., ATCC CRL-1573) was stably transfected with a hTLR9 expression construct and found  
30 to express full-length human TLR9 constitutively. The cells also contained a genomic copy of a reporter construct with a 6x NF-κB binding site and a luciferase gene reporter cassette. Incubation of the cells with CpG ODN (SEQ ID NO:1) activates NF-κB driven expression of luciferase, while incubation with medium alone (negative control) does not. The cells are

then lysed and activity of the luciferase protein determined by its catalytic activity of luciferin oxidation which is measured in a luminometer. Results are expressed as fold induction above medium control.

Assay set-up includes a reference standard material which is highly pure and well characterized. The reference material is used to create a standard curve within a defined range where the dose-response curve is linear (e.g., in the range of the EC50 value for SEQ ID NO:1, 70-100 nM). The test material is dissolved for testing and assayed at a defined concentration. Activity of the test material is calculated using the standard curve of the reference material. Quality of the tested material is deemed acceptable if activity of the test material compared to activity of the reference material falls within predetermined limits.

**Example 2. Biological Activity of Production Lot of CpG ODN (SEQ ID NO:1) Assayed Using RPMI 8226 Cells**

The assay of Example 1 is performed using RPMI 8226 cells (ATCC CCL-155) in place of the stably transfected HEK cells of Example 1. RPMI 8226 cells naturally express human TLR9. The cells are stably transfected with a 6x NF- $\kappa$ B-luciferase reporter construct. It is to be understood that the assay could also be carried out by measuring a native readout such as IL-10 secretion.

**Example 3. Expression Vectors for Human TLR3 (hTLR3) and Murine TLR3 (mTLR3)**

To create an expression vector for human TLR3, human TLR3 cDNA was amplified by the polymerase chain method (PCR) from a cDNA made from human 293 cells using the primers 5'-GAAACTCGAGCCACCATGAGACAGACTTTGCCTTGTATCTAC-3' (sense, SEQ ID NO:152) and 5'-GAAAGAATTCTTAATGTACAGAGTTTTTGGATCCAAG-3' (antisense, SEQ ID NO:153). The primers introduce *Xho*I and *Eco*RI restriction endonuclease sites at their 5' ends for use in subsequent cloning into the expression vector. The resulting amplification product fragment was cloned into pGEM-T Easy vector (Promega), isolated, cut with *Xho*I and *Eco*RI restriction endonucleases, ligated into an *Xho*I/*Eco*RI-digested pcDNA3.1 expression vector (Invitrogen). The insert was fully sequenced and translated into protein. The cDNA sequence corresponds to the published cDNA sequence for hTLR3, available as GenBank accession no. NM\_003265 (SEQ ID NO:7). The open reading frame codes for a protein 904 amino acids long, having the sequence corresponding to GenBank accession no. NP\_003256 (SEQ ID NO:8).

Corresponding nucleotide and amino acid sequences for murine TLR3 (mTLR3) are known. The nucleotide sequence of mTLR3 cDNA has been reported as GenBank accession no. AF355152 (SEQ ID NO:9), and the amino acid sequence of mTLR3 has been reported as GenBank accession no. AAK26117 (SEQ ID NO:10).

5

#### **Example 4. Reconstitution of TLR3 Signaling in 293 Fibroblasts**

Human TLR3 cDNA and murine TLR3 cDNA in pT-Adv vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the *EcoRI* site. The resulting expression vectors mentioned above were transfected into  
10 CpG-DNA non-responsive human 293 fibroblast cells (ATCC, CRL-1573) using the calcium phosphate method. Utilizing a "gain of function" assay it was possible to reconstitute human TLR3 (hTLR3) and murine TLR3 (mTLR3) signaling in 293 fibroblast cells.

Since NF- $\kappa$ B activation is central to the IL-1/TLR signal transduction pathway (Medzhitov R et al. (1998) *Mol Cell* 2:253-8; Muzio M et al. (1998) *J Exp Med*  
15 187:2097-101), in a first set of experiments human 293 fibroblast cells were transfected with hTLR3 alone or co-transfected with hTLR3 and an NF- $\kappa$ B-driven luciferase reporter construct.

Likewise, in a second set of experiments, 293 fibroblast cells were transfected with hTLR3 alone or co-transfected with hTLR3 and an IFN- $\alpha$ 4-driven luciferase reporter  
20 construct (described in Example 8 below).

In a third group of experiments, 293 fibroblast cells were transfected with hTLR3 alone or co-transfected with hTLR3 and a RANTES-driven luciferase reporter construct (described in Example 14 below).

#### **25 Example 5. Reconstitution of TLR7 Signaling**

Methods for cloning murine and human TLR7 have been described in pending U.S. Pat. Application No. 09/954,987 and corresponding published PCT application PCT/US01/29229 (WO 02/22809), both filed September 17, 2001, the contents of which are incorporated herein by reference. Human TLR7 cDNA and murine TLR7 cDNA in pT-Adv  
30 vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the *EcoRI* site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR7 (hTLR7) and murine TLR7 (mTLR7) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors

mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

#### **Example 6. Reconstitution of TLR8 Signaling**

5           Methods for cloning murine and human TLR8 have been described in pending U.S. Pat. Application No. 09/954,987 and corresponding published PCT application PCT/US01/29229 (WO 02/22809), both filed September 17, 2001, the contents of which are incorporated by reference. Human TLR8 cDNA and murine TLR8 cDNA in pT-Adv vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from  
10   Invitrogen using the EcoRI site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR8 (hTLR8) and murine TLR8 (mTLR8) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

15

#### **Example 7. Reconstitution of TLR9 Signaling in 293 Fibroblasts**

          Methods for cloning murine and human TLR9 have been described in pending U.S. Pat. Application No. 09/954,987 and corresponding published PCT application PCT/US01/29229 (WO 02/22809), both filed September 17, 2001, the contents of which are  
20   incorporated by reference. Human TLR9 cDNA and murine TLR9 cDNA in pT-Adv vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the EcoRI site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR9 (hTLR9) and murine TLR9 (mTLR9) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors  
25   mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

          To generate stable clones expressing human TLR9, murine TLR9, or either TLR9 with the NF- $\kappa$ B-luc reporter plasmid, 293 cells were transfected in 10 cm plates ( $2 \times 10^6$  cells/plate) with 16  $\mu$ g of DNA and selected with 0.7 mg/ml G418 (PAA Laboratories GmbH, Cölbe,  
30   Germany). Clones were tested for TLR9 expression by RT-PCR, for example as shown in Fig. 21. The clones were also screened for IL-8 production or NF- $\kappa$ B-luciferase activity after stimulation with ODN. Four different types of clones were generated.

293-hTLR9-luc: expressing human TLR9 and 6x NF- $\kappa$ B-luciferase reporter  
 293-mTLR9-luc: expressing murine TLR9 and 6x NF- $\kappa$ B-luciferase reporter  
 293-hTLR9: expressing human TLR9  
 293-mTLR9: expressing murine TLR9

5

Human 293 fibroblast cells were transiently transfected with hTLR9 and a 6x NF- $\kappa$ B-luciferase reporter plasmid (NF- $\kappa$ B-luc, kindly provided by Patrick Baeuerle, Munich, Germany) (Fig. 18A) or with hTLR9 alone (Fig. 18B). After stimulus with CpG-ODN (2 $\mu$ M, TCGTCGTTTTGTCGTTTTGTCGTT, SEQ ID NO:1), GpC-ODN (2 $\mu$ M, TGCTGCTTTTGTGCTTTTGTGCTT, SEQ ID NO:154), LPS (100 ng/ml) or media, NF- $\kappa$ B activation by luciferase readout (8h, Fig. 18A) or IL-8 production by ELISA (48h, Fig. 18B) was monitored. Results are representative of three independent experiments. Fig. 18 shows that cells expressing hTLR9 responded to CpG-DNA but not to LPS.

Human 293 fibroblast cells were transiently transfected with mTLR9 and the NF- $\kappa$ B-luc construct. Similar data was obtained for IL-8 production (not shown). Thus expression of TLR9 (human or mouse) in 293 cells results in a gain of function for CpG DNA stimulation similar to hTLR4 reconstitution of LPS responses.

Figs. 19 and 20 demonstrate the responsiveness of a stable 293-mTLR9-luc and 293-hTLR9-luc clones after stimulation with CpG-ODN (2 $\mu$ M, SEQ ID NO:1), GpC-ODN (2 $\mu$ M, SEQ ID NO:154), Me-CpG-ODN (2 $\mu$ M; TZGTZGTTTTGTZGTTTTGTZGTT, Z = 5-methylcytidine, SEQ ID NO:147), LPS (100 ng/ml) or media, as measured by monitoring NF- $\kappa$ B activation. Similar results were obtained utilizing IL-8 production with the stable clones. These results demonstrate that CpG-DNA non-responsive cell lines can be stably genetically complemented with TLR9 to become responsive to CpG DNA in a motif-specific manner.

#### Example 8. Method of Making IFN- $\alpha$ 4 Reporter Vector

A number of reporter vectors may be used in the practice of the invention. Some of the reporter vectors are commercially available, e.g., the luciferase reporter vectors pNF- $\kappa$ B-Luc (Stratagene) and pAP1-Luc (Stratagene). These two reporter vectors place the luciferase gene under control of an upstream (5') promoter region derived from genomic DNA for NF- $\kappa$ B or AP1, respectively. Other reporter vectors can be constructed following standard

methods using the desired promoter and a vector containing a suitable reporter, such as luciferase,  $\beta$ -galactosidase ( $\beta$ -gal), chloramphenicol acetyltransferase (CAT), and other reporters known by those skilled in the art. Following are some examples of reporter vectors constructed for use in the present invention.

5 IFN- $\alpha$ 4 is an immediate-early type 1 IFN. Sequence-specific PCR products for the -620 to +50 promoter region of IFN- $\alpha$ 4 were derived from genomic DNA of human 293 cells and cloned into the *Sma*I site of the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') -620 to +50 promoter region of IFN- $\alpha$ 4. The sequence of the -620 to +50 promoter region of IFN- $\alpha$ 4 is provided as  
10 SEQ ID NO:121.

#### **Example 9. Method of Making IFN- $\alpha$ 1 Reporter Vector**

IFN- $\alpha$ 1 is a late type 1 IFN. Sequence-specific PCR products for the -140 to +9 promoter region of IFN- $\alpha$ 1 were derived from genomic DNA of human 293 cells and cloned  
15 into *Sma*I site of the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') -140 to +9 promoter region of IFN- $\alpha$ 1. A sequence of the -140 to +9 promoter region of IFN- $\alpha$ 1 is provided as SEQ ID NO:122.

#### **Example 10. Method of Making IFN- $\beta$ Reporter Vector**

20 IFN- $\beta$  is an immediate-early type 1 IFN. The -280 to +20 promoter region of IFN- $\beta$  was derived from the pUC $\beta$ 26 vector (Algarte M et al. (1999) *J Virol* 73:2694-702) by restriction at *Eco*RI and *Taq*I sites. The 300 bp restriction fragment was filled in by Klenow enzyme and cloned into *Nhe*I-digested and filled in pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') -280  
25 to +20 promoter region of IFN- $\beta$ . A sequence of the -280 to +20 promoter region of IFN- $\beta$  is provided as SEQ ID NO:123.

#### **Example 11. Method of Making Human IL-6 Reporter Vectors**

Reporter constructs are made using the -285 to +7 promoter region derived from  
30 human IL-6 genomic DNA. (Takeshita et al. Eur. J. Immunol. 2000. 30: 108-116.) In one reporter construct the IL-6 promoter region is cloned as a *Kpn*I-*Xho*I insert into pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of



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an upstream (5') -288 to +7 promoter region derived from human IL-6 genomic DNA. A sequence of the -288 to +7 promoter region of human IL-6 is provided as SEQ ID NO:128.

The promoter can also be derived from the full-length promoter region of the IL-6 gene from -1174 to +7 (GenBank Accession No M22111) as shown below as SEQ ID  
5 NO:129.

#### **Example 12. Method of Making Human IL-8 Reporter Vectors**

Reporter constructs have been made using a -546 to +44 and a truncated -133 to +44 promoter region derived from human IL-8 genomic DNA. Mukaida N et al. (1989) *J Immunol* 143:1366-71. In each reporter construct the IL-8 promoter region was cloned as a  
10 *KpnI-XhoI* insert into pGL3-Basic Vector (Promega). One of the resulting expression vectors includes a luciferase gene under control of an upstream (5') -546 to +44 promoter region derived from human IL-8 genomic DNA. Another of the resulting expression vectors includes a luciferase gene under control of an upstream (5') -133 to +44 promoter region  
15 derived from human IL-8 genomic DNA.

The promoter can also be the upstream (5') -734 to +44 or the upstream (5') -162 to +44 promoter region derived from human IL-8 genomic DNA. Mukaida N et al. (1989) *J Immunol* 143:1366-71. A sequence of the -734 to +44 promoter region derived from human  
IL-8 is provided below as SEQ ID NO: 130.

20

#### **Example 13. Method of Making Human IL-12 p40 Reporter Vectors**

Reporter constructs have been made using truncated (-250 to +30, SEQ ID NO:127) and full length (-751 to +30, SEQ ID NO:126) promoter regions derived from human IL-12 p40 genomic DNA. (Takeshita et al. *Eur. J. Immunol.* 2000. 30: 108-116.) In one reporter  
25 construct the truncated IL-12 p40 promoter was cloned as a *KpnI-XhoI* insert into p $\beta$ gal-Basic (Promega). The resulting expression vector includes a  $\beta$  gal gene under control of an upstream (5') -250 to +30 promoter region of human IL-12 p40. In a second reporter construct the full length IL-12 p40 promoter was cloned as a *KpnI-XhoI* insert into p $\beta$ gal-Basic (Promega). The resulting expression vector includes a  $\beta$  gal gene under control  
30 of an upstream (5') -751 to +30 promoter region of human IL-12 p40. In a third reporter construct the truncated -250 to +30 promoter region of human IL-12 p40 was cloned into the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') -250 to +30 promoter region of human IL-12 p40. In a

fourth reporter construct the full length IL-12 p40 promoter of human IL-12 p40 was cloned into the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') -751 to +30 promoter region of human IL-12 p40. A sequence of the -751 to +30 promoter region of human IL-12 p40 is provided as SEQ ID NO:

5 126.

#### **Example 14. Method of Making RANTES Reporter Vector**

Transcription of the chemokine RANTES is believed to be regulated at least in part by IRF3 and by NF- $\kappa$ B. Lin R et al. (1999) *J Mol Cell Biol* 19(2):959-66; Genin P et al. (2000) *J Immunol* 164:5352-61. A 483 bp sequence-specific PCR product including the -397 to +5 promoter region of RANTES was derived from genomic DNA of human 293 cells, restricted with *Pst*I and cloned into pCAT-Basic Vector (Promega) using *Hind*III (filled in with Klenow) and *Pst*I sites (filled in). The -397 to +5 promoter region of RANTES was then isolated from the resulting RANTES/chloramphenicol acetyltransferase (CAT) reporter plasmid by restriction with *Bgl*II and *Sal*I, filled in with Klenow enzyme, and cloned into the *Nhe*I site (filled in with Klenow) of the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') -397 to +5 promoter region of RANTES. Comparison of the insert sequence -397 to +5 of Genin P et al. (2000) *J Immunol* 164:5352-61 and GenBank accession no. AB023652 (SEQ ID NO:125) revealed two point deletions (at positions 105 and 273 of SEQ ID NO:125) which do not create new restriction sites. A sequence of the -397 to +5 promoter region of RANTES is provided as SEQ ID NO:125.

#### **Example 15. RT-PCR Analysis of Cell Lines for TLR Expression**

TLR expression was determined using total RNA of cells prepared by standard methods (QIAGEN). RNA was transcribed to cDNA using AMV Reverse Transcriptase (Roche). Quantitative PCR was performed with TLR-gene specific primer sets using a LightCycler Instrument (Roche). Controls for genomic DNA impurities were performed by a similar PCR method using RNA (but without reverse transcriptase).

A variety of cell lines was screened for their expression of TLR3, 7, 8 and 9. These cell lines are A549 (human lung carcinoma), BeWo (human choriocarcinoma), HeLa (human cervix carcinoma), Hep-2 (human cervix carcinoma), KG-1 (human acute myeloid leukemia), MUTZ-3 (human acute myelomonocytic leukemia), Nalm-6 (human B cell precursor

leukemia), NK-92 (human Natural killer cell line), NK-92 MI (human Natural killer cell line, IL-2 independent), Raji (human Burkitt's lymphoma, B lymphocyte), RAMOS (Burkitt's lymphoma, B lymphocyte), RPMI 8226 (human multiple myeloma, B lymphocyte), THP-1 (human acute monocytic leukemia), U937 (human lymphoma) and Jurkat (human T cell  
 5 leukemia).

All B cell lines express, as determined by Real Time-PCR (RT-PCR), endogenous TLR9. In addition, all lines except NALM co-express TLR7. Nevertheless, none of the other cell lines appeared to express TLR7, whereas low TLR9 expression on the mRNA level was observed for KG-1 and THP-1. TLR3 appeared to be expressed in most of these cell lines,  
 10 with the highest mRNA levels for example in the NK cell lines (e.g., NK-92).

Raji cells contain high levels of TLR9 mRNA and low levels of TLR3 and TLR7 mRNA suggesting high expression of TLR9 protein and lower levels of TLR3 and TLR7 protein.

These results indicate that the cell lines expressing TLR9 can be used to screen  
 15 potential new TLR9 ligands (CpG ODN, etc.), cell lines expressing TLR7 to screen potential new TLR7 ligands (ORN (oligoribonucleotides), small molecules, etc.), and cell lines expressing both receptors may be used to screen for "hybrid" TLR7 and 9 agonists. In addition, cell lines lacking TLR8 expression (i.e., all cell lines tested) can be used to confirm the specificity of a TLR7 versus a TLR8 ligand (i.e., the latter should not be able to stimulate  
 20 TLR7-expressing cells). In contrast, cell lines expressing TLR3 (e.g., Raji cells) may be used to screen for potential new TLR3 ligands (dsRNA, etc.).

#### **Example 16. Screening of Various Cell Lines for Responses to TLR Ligands**

Except where otherwise indicated, the following general methods were used.  
 25 Cells were plated at  $5 \times 10^5$ /ml in 48 well plates in RPMI medium with 10% FBS. Stimulation was performed by addition of the oligonucleotides or other compounds diluted to the test concentrations in TE. Cells were incubated for 24 or 48h and the supernatants were taken to analyse for the presence of cytokines or chemokines.

The TLR ligands used are as follows:

30 TLR3: Poly I:C

TLR7, TLR8: R-848

TLR9:

T\*C\*C\*A\*G\*G\*A\*C\*T\*T\*C\*T\*C\*T\*C\*A\*G\*G\*T\*T (SEQ ID NO: 2);

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T\*C\*G\*T\*C\*G\*T\*T\*T\*T\*G\*T\*C\*G\*T\*T\*T\*T\*G\*T\*C\*G\*T\*T (SEQ ID NO: 1);  
 T\*G\*C\*T\*G\*C\*T\*T\*T\*T\*G\*T\*G\*C\*T\*T\*T\*T\*G\*T\*G\*C\*T\*T (SEQ ID NO: 154);  
 T\*C\*G\*T\*C\*G\*T\*T\*T\*T\*C\*G\*G\*C\*G\*C\*G\*C\*G\*C\*C\*G (SEQ ID NO: 158);  
 G\*G\*G\_G\_A\_C\_G\_A\_C\_G\_T\_C\_G\_T\_G\_G\*G\*G\*G\*G\*G (SEQ ID NO: 159);  
 5 T\*G\*C\*T\*G\*C\*T\*T\*T\*T\*C\*G\*G\*C\*G\*G\*C\*C\*G\*C\*C\*G (SEQ ID NO: 160);  
 G\*G\*G\_G\_A\_G\_C\_A\_G\_C\_T\_G\_C\_T\_G\_G\*G\*G\*G\*G\*G (SEQ ID NO: 161).  
 \* phosphorothioate linkage; \_ phosphodiester linkage.

Increased expression of cell surface markers was determined using cells stimulated as  
 10 described above and then stained with different monoclonal antibody combinations specific  
 for the cell surface markers. Analysis of the cells was performed by flow cytometry.

Changes in reporter gene activity were determined using cells transfected with a  
 NF- $\kappa$ B reporter construct (Stratagene) and a  $\beta$ -galactosidase reporter control plasmid  
 (Invitrogen) using electroporation. For NF- $\kappa$ B analysis, a 5x NF- $\kappa$ B-Luciferase Vector  
 15 (Stratagene) was used. The amount of DNA transfected as well as cell concentration was  
 varied. Stimulation was performed 24h after transfection. Cells were stimulated with the  
 indicated amounts of ODN, R-848, LPS, TNF- $\alpha$ , or IL-1  $\beta$  for the indicated incubation times.  
 Cell extracts were prepared by lysing the cells in 100  $\mu$ l reporter lysis buffer (Promega) using  
 the freeze-thaw method. All data were normalized for  $\beta$ -galactosidase expression.  
 20 Stimulation indices were calculated in reference to luciferase activity of medium without  
 addition of ODN.

Stimulation of the Raji cell line with a TLR9 ligand (CpG ODN), a TLR3 ligand (poly  
 I:C) or a TLR7 ligand (R-848) results in the ligand-specific secretion of cytokines. Figs. 14  
 and 15 show IL-6 production of Raji cells upon stimulation with ODN, poly I:C or R-848.  
 25 Fig. 16 shows IFN- $\alpha$ 2 production of Raji cells upon stimulation with ODN, poly I:C or R-848.  
 In all assays, cells were incubated with Na-Butyrate for 48h before stimulation with TLR  
 ligands. CpG stimulation of the RAMOS cell lines can result in the CpG-specific up-  
 regulation of cell surface markers such as CD80, as shown in Fig. 17.

### 30 **Example 17. Inhibition of a Positive Reference Compound Response with an Inhibitory Test Compound**

Inhibition of CpG mediated chemokine production was determined using RPMI 8226  
 cells incubated with increasing amounts of SEQ ID NO:1 in the presence of an

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immunoinhibitory ODN (SEQ ID NO: 151). IP-10 production was measured 24h later by ELISA (Fig. 9).

### Equivalents

5           The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described  
10   herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention.

          All references, patents and patent publications that are recited in this application are incorporated in their entirety herein by reference.

15

We claim:

Claims

1. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising  
contacting an RPMI 8226 cell that expresses a TLR with a test compound and  
5 measuring a test level of TLR signaling activity,  
wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and  
wherein the TLR signaling activity is selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-8 expression, IL-8 production, IL-8  
10 secretion, IL-10 expression, IL-10 production, IL-10 secretion, IP-10 expression, IP-10 production, IP-10 secretion, TNF- $\alpha$  expression, TNF- $\alpha$  production and TNF- $\alpha$  secretion.
2. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising  
15 contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,  
wherein a test level that is positive is indicative of an immunostimulatory compound, and  
wherein the cell is a Raji cell, a RAMOS cell, a Nalm cell, a THP-1 cell, or a KG-  
20 1 cell.
3. The method of claim 1 or 2, wherein the test level is positive relative to a reference level determined by contacting the cell with a reference compound and measuring a reference TLR signaling activity.  
25
4. The method of claim 3, wherein the reference compound is a positive reference compound
5. The method of claim 4, wherein the positive reference compound is  
30 selected from the group consisting of an immunostimulatory nucleic acid and an imidazoquinoline compound.

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6. The method of claim 3, wherein the reference compound is a negative reference compound.

7. The method of claim 6, wherein the negative reference compound is  
5 medium alone.

8. The method of claim 5, wherein the immunostimulatory nucleic acid is selected from the group consisting of a CpG nucleic acid, a T-rich nucleic acid, a poly-T nucleic acid and a poly-G nucleic acid.

10

9. The method of claim 5, wherein the imidazoquinoline compound is selected from the group consisting of R-848 and R-847.

10. The method of claim 1 or 2, wherein the test compound is a nucleic  
15 acid.

11. The method of claim 10, wherein the nucleic acid does not comprise a motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a poly-G motif.

20

12. The method of claim 10, wherein the nucleic acid comprises a phosphorothioate backbone linkage.

13. The method of claim 10, wherein the nucleic acid is a DNA, an RNA or  
25 a DNA-RNA hybrid.

14. The method of claim 1 or 2, wherein the test compound is a non-nucleic acid small molecule.

15. The method of claim 1 or 2, wherein the test compound comprises an  
30 amino acid, a carbohydrate, a lipid, or a hormone.

16. The method of claim 15, wherein the carbohydrate is a polysaccharide.

17. The method of claim 1 or 2, wherein the test compound is derived from a molecular library.
- 5 18. The method of claim 1, wherein the cell is transfected with a nucleic acid.
19. The method of claim 18, wherein the nucleic acid encodes a TLR or a reporter construct.
- 10 20. The method of claim 2, wherein the cell is transfected with a nucleic acid.
21. The method of claim 20, wherein the nucleic acid encodes a TLR or a reporter construct.
- 15 22. The method of claim 19 or 21, wherein the TLR is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9 and TLR10.
- 20 23. The method of claim 22, wherein the TLR is a human TLR.
24. The method of claim 19 or 21, wherein the reporter construct is selected from the group consisting of a luciferase reporter construct, a  $\beta$ -galactosidase reporter construct, a chloramphenicol acetyltransferase reporter construct, a green fluorescent protein reporter construct, and a secreted alkaline phosphatase construct.
- 25 25. The method of claim 19 or 21, wherein the reporter construct comprises a TLR responsive promoter.
- 30 26. The method of claim 25, wherein the TLR responsive promoter comprises a transcription factor binding site selected from the group consisting of a NF- $\kappa$ B binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an



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IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE.

27. The method of claim 25, wherein the TLR responsive promoter is a  
5 promoter region selected from the group consisting of an IL-1 promoter region, an IL-6  
promoter region, an IL-8 promoter region, an IL-10 promoter region, an IL-12 p40 promoter  
region, an IFN- $\alpha$ 1 promoter region, an IFN- $\alpha$ 4 promoter region, an IFN- $\beta$  promoter region, an  
IFN- $\gamma$  promoter region, a TNF- $\alpha$  promoter region, a TNF- $\beta$  promoter region, an IP-9 promoter  
region, an IP-10 promoter region, a RANTES promoter region, an ITAC promoter region, a  
10 MCP-1 promoter region, an IGFBP4 promoter region, a CD54 promoter region, a CD69  
promoter region, a CD71 promoter region, a CD80 promoter region, a CD86 promoter region,  
a HLA-DR promoter region, and a HLA class I promoter region.

28. The method of claim 18 or 20, wherein the cell is stably transfected.  
15

29. The method of claim 1 or 2, wherein the TLR signaling activity is  
measured by cytokine secretion or chemokine secretion.

30. The method of claim 1, wherein the TLR signaling activity is selected  
20 from the group consisting of IL-8 secretion, IL-10 secretion, IP-10 secretion and TNF- $\alpha$   
secretion.

31. The method of claim 2, wherein the TLR signaling activity is selected  
from the group consisting of IL-6 expression, IL-6 production, IL-6 secretion, IL-8  
25 expression, IL-8 production, IL-8 secretion, IL-10 expression, IL-10 production, IL-10  
secretion, IP-10 expression, IP-10 production, IP-10 secretion, IL-12 expression, IL-12  
production, IL-12 secretion, TNF- $\alpha$  expression, TNF- $\alpha$  production and TNF- $\alpha$  secretion.

32. The method of claim 2, wherein the TLR signaling activity is measured  
30 by phosphorylation.

33. The method of claim 32, wherein phosphorylation is total cellular  
phosphorylation.

34. The method of claim 32, wherein phosphorylation is phosphorylation of a factor selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, NFkB subunits, c-Jun and c-Fos.

5

35. The method of claim 1 or 2, wherein the TLR signaling activity is measured by gene expression.

36. The method of claim 1, wherein the TLR signaling activity is measured  
10 by gene expression selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-8 expression, IL-10 expression, IP-10 expression, and TNF- $\alpha$  expression.

37. The method of claim 35, wherein TLR signaling activity is measured  
15 by microarray techniques.

38. The method of claim 2, wherein the TLR signaling activity is measured by cell proliferation.

20 39. The method of claim 1 or 2, wherein TLR signaling activity is measured by cell surface marker expression.

40. The method of claim 1, wherein TLR signaling activity is measured by cell surface expression of CD71, CD86 or HLA-DR.

25

41. The method of claim 2, wherein TLR signaling activity is measured by CD71 cell surface expression, CD86 cell surface expression, HLA-DR cell surface expression, CD80 cell surface expression, HLA class I cell surface expression, CD54 cell surface expression and CD69 cell surface expression.

30

42. The method of claim 2, wherein TLR signaling activity is measured by antibody secretion.

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43. The method of claim 42, wherein the antibody secretion is IgM secretion.

44. A composition comprising  
an RPMI 8226 cell stably transfected with a nucleic acid encoding a TLR  
5 polypeptide, or a fragment thereof.

45. The composition of claim 44, further comprising a reporter construct  
comprising a promoter and a reporter sequence wherein the promoter is a TLR responsive  
promoter.  
10

46. The composition of claim 45, wherein the TLR responsive promoter  
comprises a nucleic acid sequence selected from the group consisting of an NF- $\kappa$ B binding  
site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3  
binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding  
15 site, and a TARE.

47. The composition of claim 45, wherein the reporter sequence is selected  
from the group consisting of a luciferase sequence, a  $\beta$ -galactosidase sequence, a green  
fluorescent protein sequence, a secreted alkaline phosphatase sequence and a chloramphenicol  
20 transferase sequence.

48. The composition of claim 44, wherein the TLR polypeptide or fragment  
thereof is a human TLR polypeptide or fragment thereof.

49. The composition of claim 44, wherein the TLR polypeptide or fragment  
thereof is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6,  
TLR7, TLR8, TLR9 and TLR10.  
25

50. The composition of claim 44, wherein the TLR polypeptide or fragment  
30 thereof is a human TLR polypeptide.

51. A screening method for identifying agonists of Toll-like receptor (TLR)  
signaling activity, comprising

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contacting an cell that ectopically expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

5            wherein the cell that ectopically expresses a TLR is selected from the group consisting of RPMI 8226, RAMOS, Raji, Nalm, THP-1, KG-1 and 293 HEK.

52.            The method of claim 51, wherein the test level is positive relative to a reference level determined by contacting the cell with a reference compound and measuring a  
10            reference TLR signaling activity.

53.            The method of claim 52, wherein the reference compound is a positive reference compound.

15            54.            The method of claim 53, wherein the positive reference compound is selected from the group consisting of an immunostimulatory nucleic acid and an imidazoquinoline compound.

20            55.            The method of claim 54, wherein the immunostimulatory nucleic acid is selected from the group consisting of a CpG nucleic acid, a T-rich nucleic acid, a poly-T nucleic acid and a poly-G nucleic acid.

25            56.            The method of claim 54, wherein the imidazoquinoline compound is selected from the group consisting of R-848 and R-847.

57.            The method of claim 52, wherein the reference compound is negative reference compound.

30            58.            The method of claim 57, wherein the negative reference compound is medium alone.

59.            The method of claim 51, wherein the test compound is a nucleic acid.

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60. The method of claim 59, wherein the nucleic acid does not comprise a motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a poly-G motif.

5 61. The method of claim 59, wherein the nucleic acid comprises a phosphorothioate backbone linkage.

62. The method of claim 59, wherein the nucleic acid is a DNA, an RNA, or a DNA-RNA hybrid.

10

63. The method of claim 51, wherein the test compound is a non-nucleic acid small molecule.

64. The method of claim 51, wherein the test compound comprises an  
15 amino acid, a carbohydrate, a lipid, or a hormone.

65. The method of claim 64, wherein the carbohydrate is a polysaccharide.

66. The method of claim 51, wherein the test compound is derived from a  
20 molecular library.

67. The method of claim 51, wherein the TLR signaling activity is selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-6 expression, IL-6 production, IL-6 secretion, IL-8 expression, IL-8 production, IL-8 secretion,  
25 IL-10 expression, IL-10 production, IL-10 secretion, IL-12 expression, IL-12 production, IL-12 secretion, IP-10 expression, IP-10 production, IP-10 secretion, TNF- $\alpha$  expression, TNF- $\alpha$  production and TNF- $\alpha$  secretion.

68. The method of claim 51, wherein the TLR is selected from the group  
30 consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9 and TLR10.

69. The method of claim 51, wherein the TLR is a human TLR.

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70. The method of claim 51, wherein the cell is transfected with a reporter construct.

71. The method of claim 70, wherein the reporter construct is selected from the group consisting of a luciferase reporter construct, a  $\beta$ -galactosidase reporter construct, a chloramphenicol acetyltransferase reporter construct, a green fluorescent protein reporter construct, and a secreted alkaline phosphatase construct.

72. The method of claim 71, wherein the TLR signaling activity is measured by luciferase expression,  $\beta$ -galactosidase expression, chloramphenicol expression, acetyltransferase expression, green fluorescent protein expression, alkaline phosphatase expression and alkaline phosphatase secretion.

73. The method of claim 71, wherein the reporter construct comprises a TLR responsive promoter.

74. The method of claim 25 or 73, wherein the TLR responsive promoter is a TLR1 responsive promoter, a TLR2 responsive promoter, a TLR3 responsive promoter, a TLR4 responsive promoter, a TLR5 responsive promoter, a TLR6 responsive promoter, a TLR7 responsive promoter, a TLR8 responsive promoter, a TLR9 responsive promoter and a TLR10 responsive promoter.

75. The method of claim 73, wherein the TLR responsive promoter comprises a transcription factor binding site selected from the group consisting of an NF- $\kappa$ B binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE.

76. The method of claim 73, wherein the TLR responsive promoter is a promoter region selected from the group consisting of an IL-1 promoter region, an IL-6 promoter region, an IL-8 promoter region, an IL-10 promoter region, an IL-12 p40 promoter region, an IFN- $\alpha$ 1 promoter region, an IFN- $\alpha$ 4 promoter region, an IFN- $\beta$  promoter region, an IFN- $\gamma$  promoter region, a TNF- $\alpha$  promoter region, a TNF- $\beta$  promoter region, an IP-9 promoter

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region, an IP-10 promoter region, a RANTES promoter region, an ITAC promoter region, a MCP-1 promoter region, an IGFBP4 promoter region, a CD54 promoter region, a CD69 promoter region, a CD71 promoter region, a CD80 promoter region, a CD86 promoter region, a HLA-DR promoter region, and a HLA class I promoter region.

5

77. The method of claim 51, wherein the cell is stably transfected with a TLR nucleic acid.

78. The method of claim 70, wherein the cell is stably transfected with the  
10 reporter construct.

79. The method of claim 51, wherein the TLR signaling activity is measured by cytokine secretion or chemokine secretion.

80. The method of claim 79, wherein the cytokine secretion or chemokine  
15 secretion is selected from the group consisting of IL-8 secretion, TNF- $\alpha$  secretion, IL-10 secretion and IP-10 secretion.

81. The method of claim 79, wherein the cytokine secretion or chemokine  
20 secretion is selected from the group consisting of IL-6 secretion and IL-12 secretion.

82. The method of claim 51, wherein the TLR signaling activity is measured by phosphorylation.

83. The method of claim 82, wherein phosphorylation is total cellular  
25 phosphorylation.

84. The method of claim 82, wherein phosphorylation is phosphorylation  
of a factor selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, NF- $\kappa$ B  
30 subunits, c-Jun and c-Fos.

85. The method of claim 51, wherein the TLR signaling activity is measured by gene expression.

86. The method of claim 85, wherein the gene expression is selected from the group consisting of IL-8 expression, IL-10 expression, IP-10 expression, CD71 expression, CD86 expression and HLA-DR expression.

5

87. The method of claim 85, wherein the gene expression is selected from the group consisting of IL-6 expression, IL-12 expression and TNF- $\alpha$  expression.

88. The method of claim 51, wherein the TLR signaling activity is measured by microarray techniques.

10

89. The method of claim 51, wherein the TLR signaling activity is measured by cell proliferation.

90. The method of claim 51, wherein the TLR signaling activity is measured by cell surface marker expression.

15

91. The method of claim 90, wherein the cell surface marker expression is selected from the group consisting of CD71 cell surface expression, CD86 cell surface expression and HLA-DR cell surface expression.

20

92. The method of claim 90, wherein the cell surface marker expression is selected from the group consisting of CD80 cell surface expression, HLA class I cell surface expression, CD54 cell surface expression and CD69 cell surface expression.

25

93. The method of claim 51, wherein the TLR signaling activity is measured by antibody secretion.

94. The method of claim 93, wherein the antibody secretion is IgM secretion.

30

95. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising



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contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

5            wherein a test level that is less than a reference level is indicative of test compound that is a TLR antagonist, and

             wherein the cell is selected from the group consisting of a RPMI 8226 cell, a RAMOS cell, a Raji cell, a THP-1 cell, a Nalm cell and a KG-1 cell.

10            96.            The method of claim 95, wherein the positive reference compound is selected from the group consisting of an immunostimulatory nucleic acid and an immunostimulatory imidazoquinoline compound.

             97.            The method of claim 96, wherein the immunostimulatory nucleic acid  
15 is selected from the group consisting of a CpG nucleic acid, a T-rich nucleic acid, a poly-T nucleic acid and a poly-G nucleic acid.

             98.            The method of claim 96, wherein the imidazoquinoline compound is selected from the group consisting of R-848 and R-847.

20            99.            The method of claim 95, wherein the test compound is a nucleic acid.

             100.           The method of claim 99, wherein the nucleic acid does not comprise a motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a  
25 poly-G motif.

             101.           The method of claim 99, wherein the nucleic acid comprises a phosphorothioate backbone linkage.

30            102.           The method of claim 99, wherein the nucleic acid is a DNA, an RNA or a DNA-RNA hybrid.

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103. The method of claim 95, wherein the test compound is a non-nucleic acid small molecule.
104. The method of claim 95, wherein the test compound comprises an amino acid, a carbohydrate, a lipid, or a hormone.
105. The method of claim 104, wherein the carbohydrate is a polysaccharide.
106. The method of claim 95, wherein the test compound is derived from a molecular library.
107. The method of claim 95, wherein the experimental cell is transfected with a nucleic acid.
108. The method of claim 107, wherein the nucleic acid encodes a TLR or a reporter construct.
109. The method of claim 108, wherein the TLR is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9 and TLR10.
110. The method of claim 108, wherein the TLR is a human TLR.
111. The method of claim 108, wherein the reporter construct is selected from the group consisting of a luciferase reporter construct, a  $\beta$ -galactosidase reporter construct, a chloramphenicol acetyltransferase reporter construct, a green fluorescent protein reporter construct, and a secreted alkaline phosphatase construct.
112. The method of claim 111, wherein the TLR signaling activity is selected from the group consisting of luciferase expression,  $\beta$ -galactosidase expression, chloramphenicol acetyltransferase expression, green fluorescent protein expression, alkaline phosphatase expression and alkaline phosphatase secretion.

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113. The method of claim 108, wherein the reporter construct comprises a TLR responsive promoter.

114. The method of claim 113, wherein the TLR responsive promoter  
5 comprises a transcription factor binding site selected from the group consisting of an NF- $\kappa$ B binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE.

10 115. The method of claim 113, wherein the TLR responsive promoter is a promoter region selected from the group consisting of an IL-1 promoter region, an IL-6 promoter region, an IL-8 promoter region, an IL-10 promoter region, an IL-12 p40 promoter region, an IFN- $\alpha$ 1 promoter region, an IFN- $\alpha$ 4 promoter region, an IFN- $\beta$  promoter region, an IFN- $\gamma$  promoter region, a TNF- $\alpha$  promoter region, a TNF- $\beta$  promoter region, an IP-9 promoter  
15 region, an IP-10 promoter region, a RANTES promoter region, an ITAC promoter region, a MCP-1 promoter region, an IGFBP4 promoter region, a CD54 promoter region, a CD69 promoter region, a CD71 promoter region, a CD80 promoter region, a CD86 promoter region, a HLA-DR promoter region, and a HLA class I promoter region.

20 116. The method of claim 113, wherein the TLR responsive promoter is selected from the group consisting of a TLR1 responsive promoter, TLR2 responsive promoter, a TLR3 responsive promoter, a TLR4 responsive promoter, a TLR5 responsive promoter, a TLR6 responsive promoter, a TLR7 responsive promoter, a TLR8 responsive promoter, a TLR9 responsive promoter and a TLR10 responsive promoter.

25

117. The method of claim 107, wherein the cell is stably transfected with the nucleic acid.

118. The method of claim 95, wherein the TLR signaling activity is  
30 measured by cytokine secretion or chemokine secretion.

119. The method of claim 118, wherein the cytokine secretion or chemokine secretion is selected from the group consisting of IL-6 secretion, IL-12 secretion and TNF- $\alpha$  secretion.

5 120. The method of claim 118, wherein the cytokine secretion or chemokine secretion is selected from the group consisting of IL-8 secretion, IL-10 secretion and IP-10 secretion.

10 121. The method of claim 95, wherein the TLR signaling activity is measured by phosphorylation.

122. The method of claim 121, wherein phosphorylation is total cellular phosphorylation.

15 123. The method of claim 122, wherein phosphorylation is phosphorylation of a factor selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, NF- $\kappa$ B subunits, c-Jun and c-Fos.

20 124. The method of claim 95, wherein the TLR signaling activity is measured by gene expression.

25 125. The method of claim 124, wherein the gene expression is selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-8 expression, IL-10 expression and IP-10 expression.

126. The method of claim 124, wherein the gene expression is selected from the group consisting of IL-6 expression, IL-12 expression and TNF- $\alpha$  expression.

30 127. The method of claim 95, wherein the TLR signaling activity is measured by microarray techniques.

128. The method of claim 95, wherein the TLR signaling activity is measured by cell proliferation.

129. The method of claim 95, wherein the TLR signaling activity is measured by cell surface marker expression.

5 130. The method of claim 129, wherein the cell surface marker expression is selected from the group consisting of CD71 cell surface expression, CD86 cell surface expression and HLA-DR MHC class II cell surface expression.

10 131. The method of claim 129, wherein the cell surface marker expression is selected from the group consisting of CD80 cell surface expression, HLA class I cell surface expression, CD54 cell surface expression and CD69 cell surface expression.

15 132. The method of claim 95, wherein the TLR signaling activity is measured by antibody secretion.

133. The method of claim 132, wherein the antibody secretion is IgM secretion.

20 134. The method of claim 95, wherein the cell is contacted to the positive reference compound and the test compound simultaneously.

135. The method of claim 95, wherein the cell is contacted to the positive reference compound prior to contact with the test compound.

25 136. The method of claim 95, wherein the cell is contacted to the test compound prior to contact with the positive reference compound.

30 137. A method for quality assessment of a test composition containing a known Toll like receptor (TLR) ligand, comprising:  
measuring a reference activity of a reference composition comprising a known TLR ligand, wherein the known TLR ligand is a nucleic acid molecule;  
measuring a test activity of a test composition comprising the known TLR ligand; and  
comparing the test activity to the reference activity.

138. The method of claim 137, further comprising selecting the test composition if the test activity falls within a predetermined range of variance about the reference activity.

5

139. The method of claim 1, wherein the reference composition is a first production lot of a pharmaceutical composition comprising the known TLR ligand, and wherein the test composition is a second production lot of a pharmaceutical composition comprising the known TLR ligand.

10

140. The method of claim 137, wherein the reference composition is a first in-process lot of a composition comprising the known TLR ligand, and wherein the test composition is a second in-process lot of a composition comprising the known TLR ligand.

15

141. The method of claim 137, wherein the measuring the reference activity comprises contacting the reference composition with an isolated cell expressing a TLR responsive to the known TLR ligand, and wherein the measuring the test activity comprises contacting the test composition with the isolated cell expressing a TLR responsive to the known TLR ligand.

20

142. The method of claim 141, wherein the isolated cell expressing the TLR responsive to the known TLR ligand comprises an expression vector for the TLR responsive to the known TLR ligand.

25

143. The method of claim 141, wherein the isolated cell expressing the TLR responsive to the known TLR ligand naturally expresses the TLR responsive to the known TLR ligand.

30

144. The method of claim 141, wherein the isolated cell expressing the TLR responsive to the known TLR ligand is RPMI 8226.

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145. The method of claim 137, wherein the measuring the reference activity and the measuring the test activity each comprise measuring signaling activity mediated by a TLR responsive to the known TLR ligand.

5 146. The method of claim 145, wherein the signaling activity is activity of a reporter construct under control of NF- $\kappa$ B response element.

147. The method of claim 145, wherein the signaling activity is activity of a reporter construct under control of interferon-stimulated response element (ISRE).

10

148. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IFN- $\alpha$  promoter.

149. The method of claim 145, wherein the signaling activity is activity of a  
15 reporter gene under control of an IFN- $\beta$  promoter.

150. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IL-6 promoter.

20 151. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IL-8 promoter.

152. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IL-12 p40 promoter.

25

153. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of a RANTES promoter.

154. The method of claim 137, wherein the known TLR ligand is a TLR9  
30 ligand.

155. The method of claim 137, wherein the known TLR ligand is a TLR3 ligand.

156. The method of claim 137, wherein the known TLR ligand is a TLR7 ligand.

5 157. The method of claim 137, wherein the known TLR ligand is a TLR8 ligand.

158. The method of claim 137, wherein the known TLR ligand is an immunostimulatory nucleic acid.

10 159. The method of claim 137, wherein the known TLR ligand is a CpG nucleic acid.

15 160. The method of claim 137, wherein the known TLR ligand is an immunoinhibitory nucleic acid.

161. A method for quality assessment of a test lot of a pharmaceutical product containing a known TLR9 ligand, comprising:  
measuring a reference activity of a reference lot of a pharmaceutical product  
20 comprising a known TLR9 ligand, wherein the known TLR9 ligand is a nucleic acid molecule;  
measuring a test activity of a test lot of a pharmaceutical product comprising the known TLR9 ligand;  
comparing the test activity to the reference activity; and  
25 rejecting the test lot if the test activity falls outside of a predetermined range of variance about the reference activity.

162. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence TCGTCGTTTTGTCGTTTTGTCGTT (SEQ ID  
30 NO:1).



163. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTGACGTTTTGTCGTT-3' (SEQ ID NO:139).

5 164. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTGTCGTTTTTTTCGA-3' (SEQ ID NO:140).

10 165. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTCGTCGTTTCGTCGTT-3' (SEQ ID NO:141).

15 166. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTCGTCGTTTTGTCGTT-3' (SEQ ID NO:142).

20 167. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTTCGGTCGTTTT-3' (SEQ ID NO:143).

168. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTTCGTGCGTTTTT-3' (SEQ ID NO:144).

25 169. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTCGGCGGCCGCCG-3' (SEQ ID NO:145).

30 170. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTC\_GTTTTAC\_GGCGCC\_GTGCCG-3' (SEQ ID NO:146), wherein every internucleoside linkage is phosphorothioate except for those indicated by “\_”, which are phosphodiester.

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171. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

5 wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

wherein the cell is a Raji cell, a RAMOS cell, a Nalm cell, a THP-1 cell, or a KG-1 cell, and the TLR is TLR9.

10 172. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

15 wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

wherein the cell is a Raji cell or a RAMOS cell, and the TLR is TLR7.

173. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

20 contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

25 wherein the cell is a Raji cell, a RAMOS cell, a KG-1 cell, a Nalm-6 cell, a Jurkat cell, a Hela cell, a Hep-2 cell, an A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell, and the TLR is TLR3.

174. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising

30 contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

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wherein a test level that is less than a reference level is indicative of a test compound that is a TLR antagonist, and

wherein the cell is selected from the group consisting of a RPMI 8226 cell, a RAMOS cell, a Raji cell, a THP-1 cell, a Nalm cell and a KG-1 cell, and the TLR is TLR9.

5

175. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

10

contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

wherein a test level that is less than a reference level is indicative of a test compound that is a TLR antagonist, and

15 wherein the cell is selected from the group consisting of a RPMI 8226 cell, a RAMOS cell and a Raji cell, and the TLR is TLR7.

175. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising

20 contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

wherein a test level that is less than a reference level is indicative of a test compound that is a TLR antagonist, and

25

wherein the cell is selected from the group consisting of a Raji cell, a RAMOS cell, a KG-1 cell, a Nalm-6 cell, a Jurkat cell, a Hela cell, a Hep-2 cell, an A549 cell, a Bewo cell, an NK-92 cell and an NK-92 MI cell, and the TLR is TLR3.

176. A screening method for identifying an enhancer of a Toll-like receptor (TLR) agonist, comprising

30

contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity, and

contacting a cell with the positive reference compound and a test compound and measuring a test level of TLR signaling activity,

wherein the positive reference compound is a TLR agonist, and a test level that is greater than the reference level is indicative of a test compound that is an enhancer of a TLR agonist.

177. The method of claim 176, wherein the positive reference compound is an immunostimulatory nucleic acid.

178. The method of claim 176, wherein the positive reference compound is an imidazoquinoline compound.

180. The method of claim 176, wherein the cell is selected from the group consisting of a KG-1 cell, a Nalm-6 cell, a Raji cell, a RAMOS cell, a Jurkat cell, a HeLa cell, a Hep-2 cell, an A549 cell, a Bewo cell, an NK-92 cell and an NK-92 MI cell, and the TLR is TLR3.

181. The method of claim 176, wherein the cell is selected from the group consisting of a KG-1 cell, a Nalm-6 cell, a Raji cell, an RPMI 8226 cell, a RAMOS cell, and a THP-1 cell, and the TLR is TLR9.

182. The method of claim 176, wherein the cell is selected from the group consisting of a Raji cell, an RPMI 8226 cell and a RAMOS cell, and the TLR is TLR7.

183. The method of claim 1, wherein the TLR is TLR7 or TLR9.

184. The method of claim 172-175 or 176, wherein the cell is unmodified.

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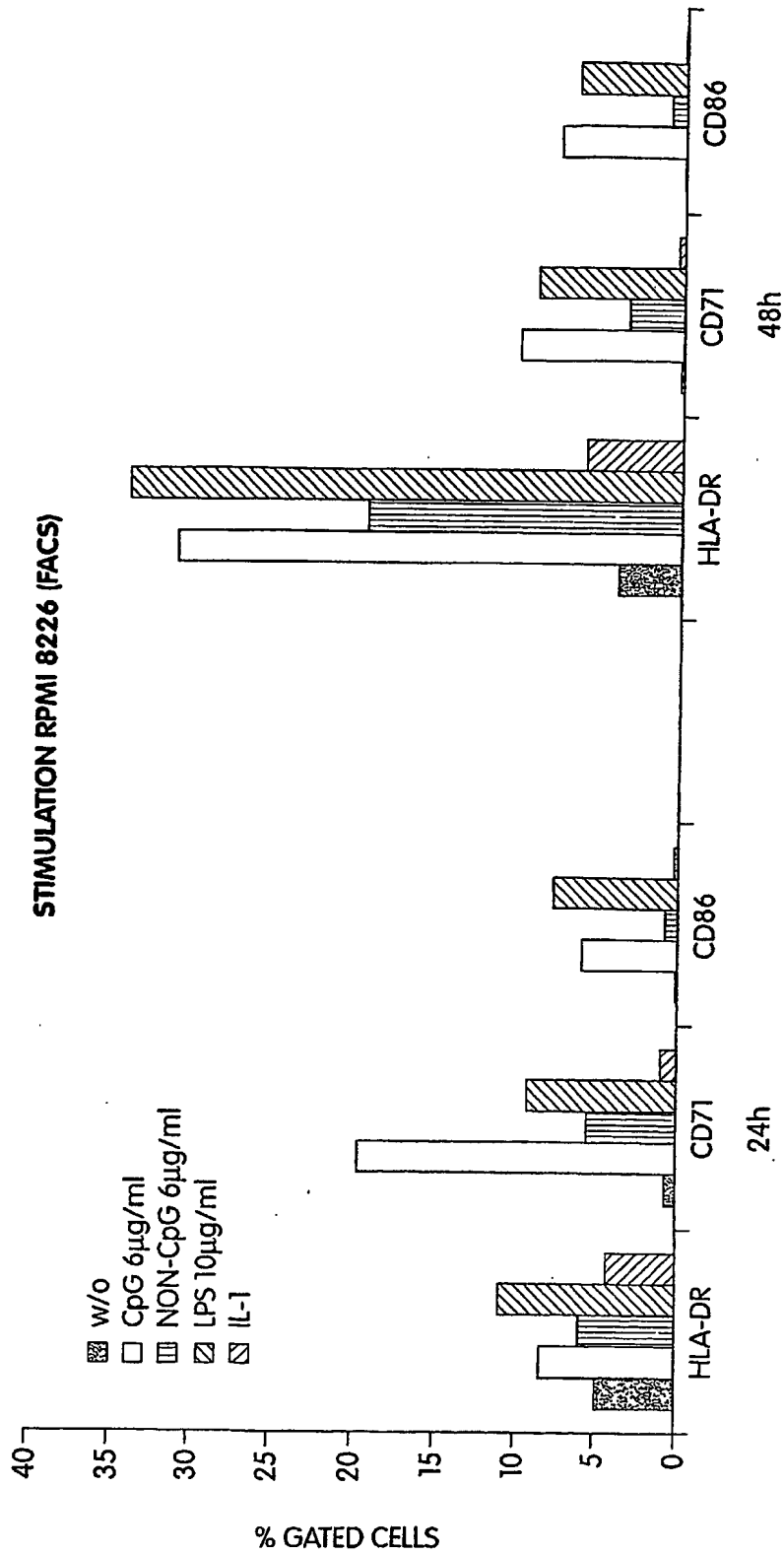


Fig. 1

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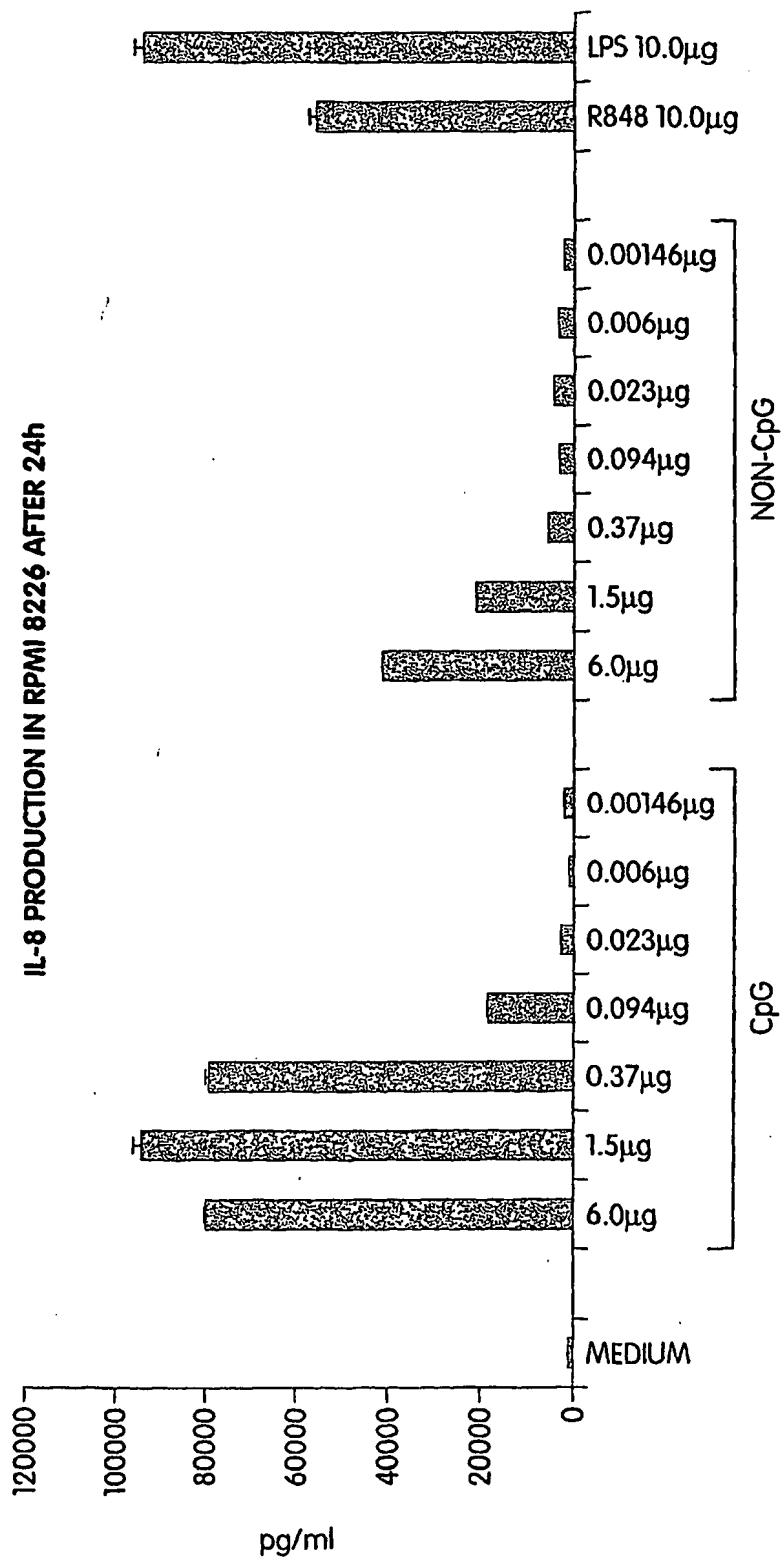


Fig. 2

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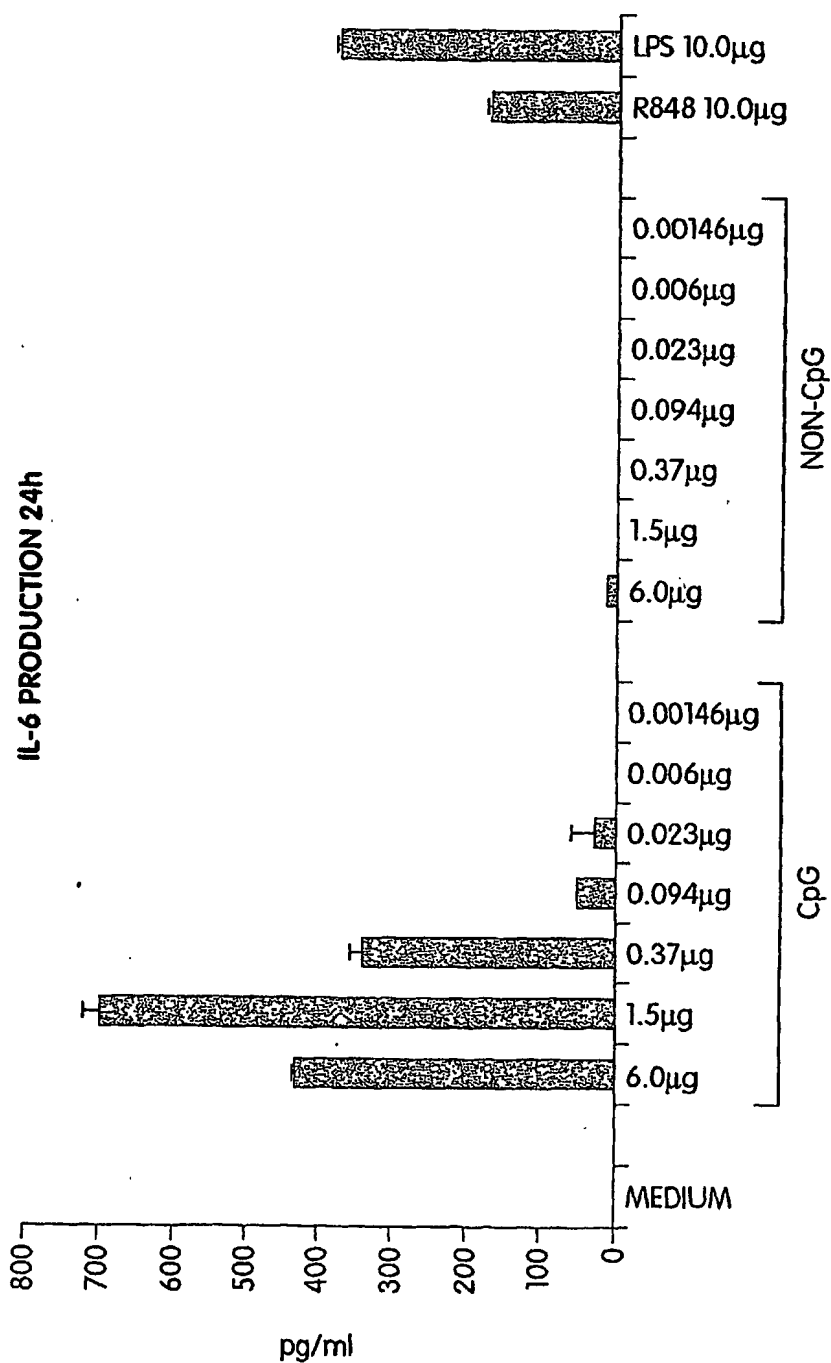


Fig. 3

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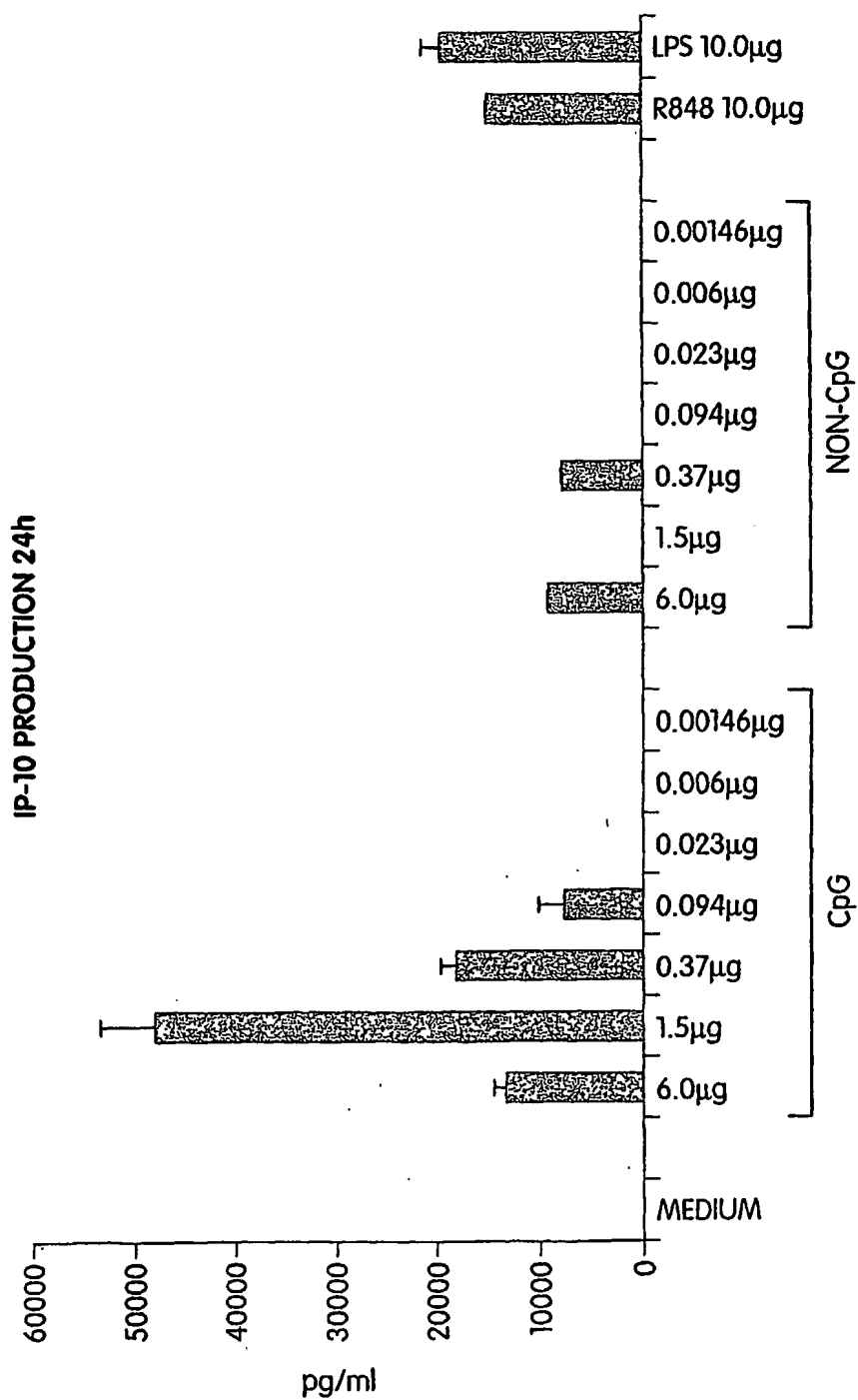


Fig. 4



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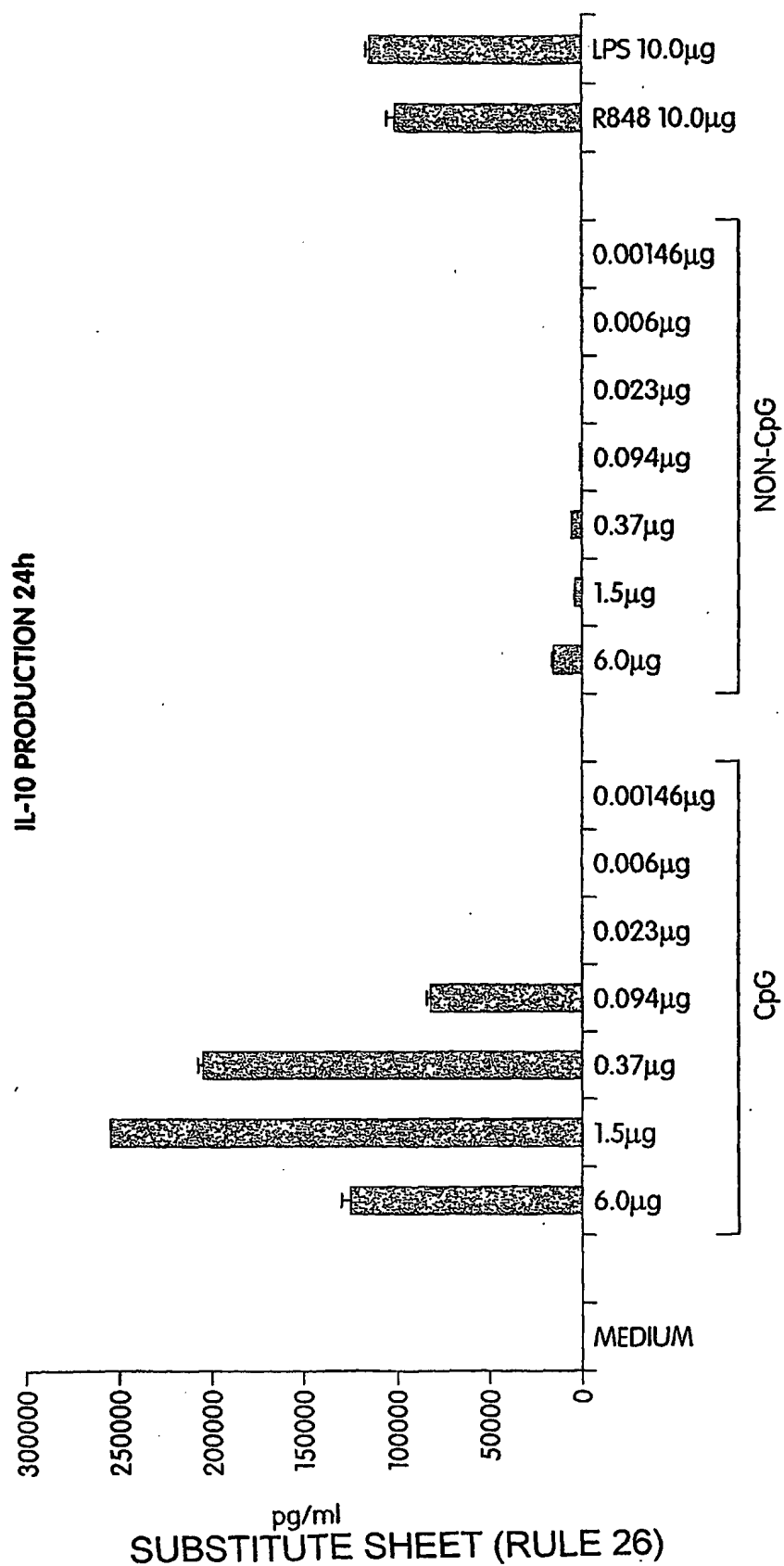


Fig. 5

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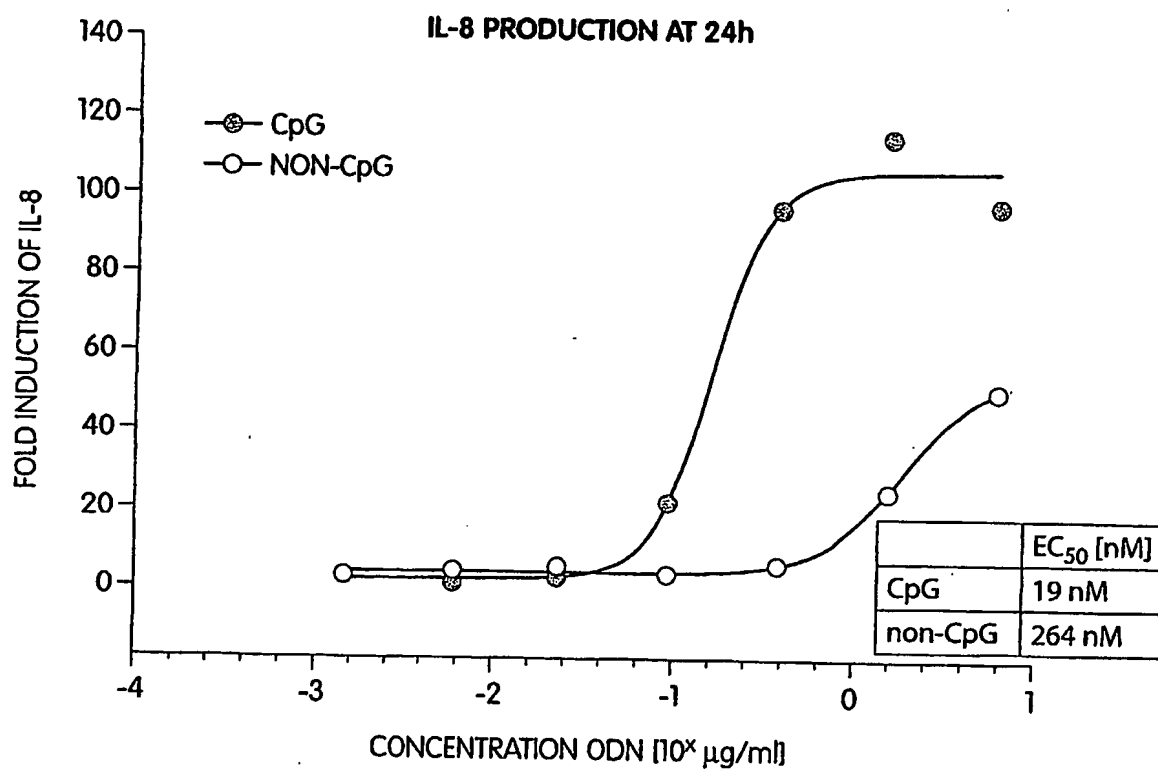


Fig. 6

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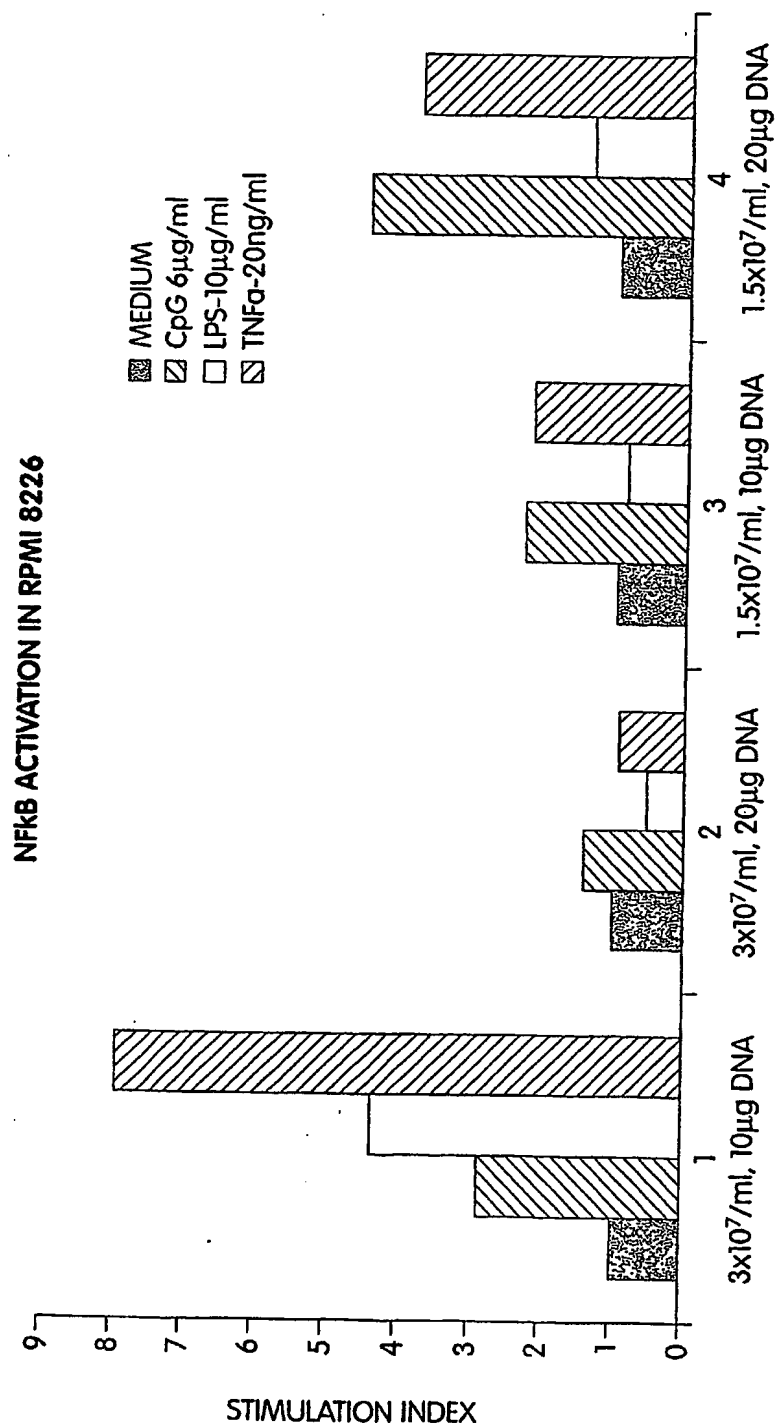


Fig. 7

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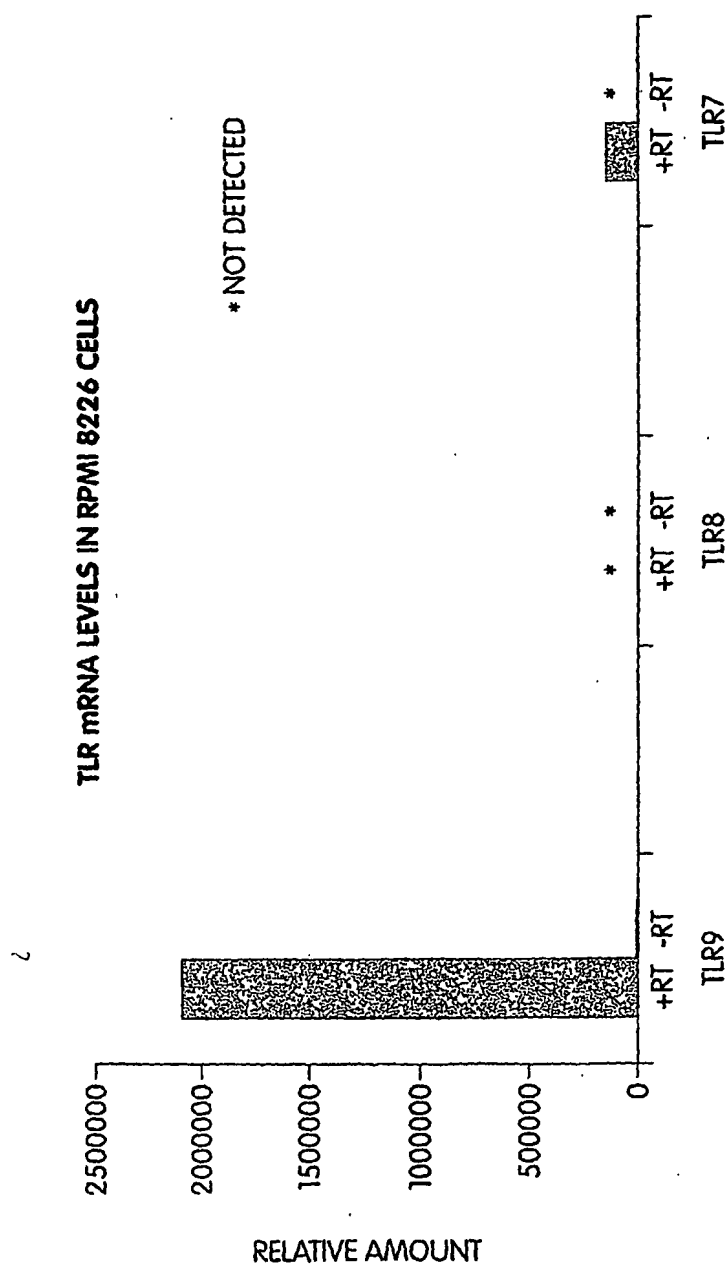


Fig. 8

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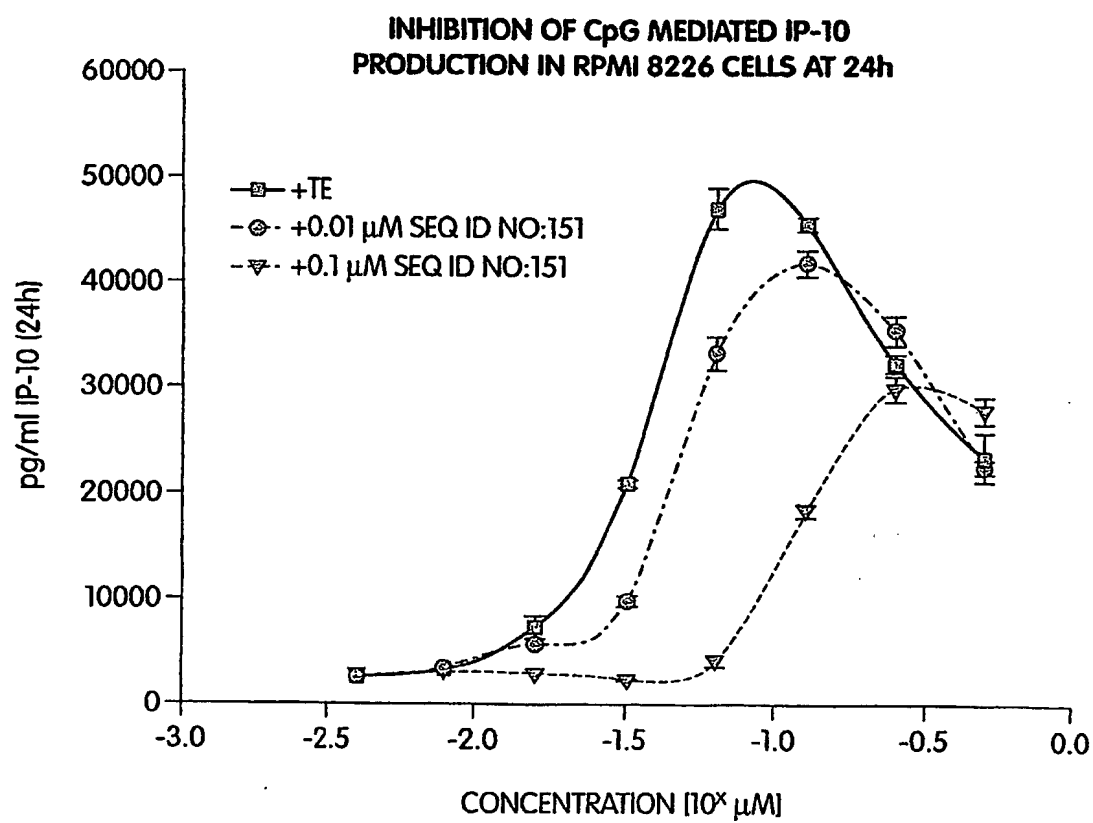


Fig. 9

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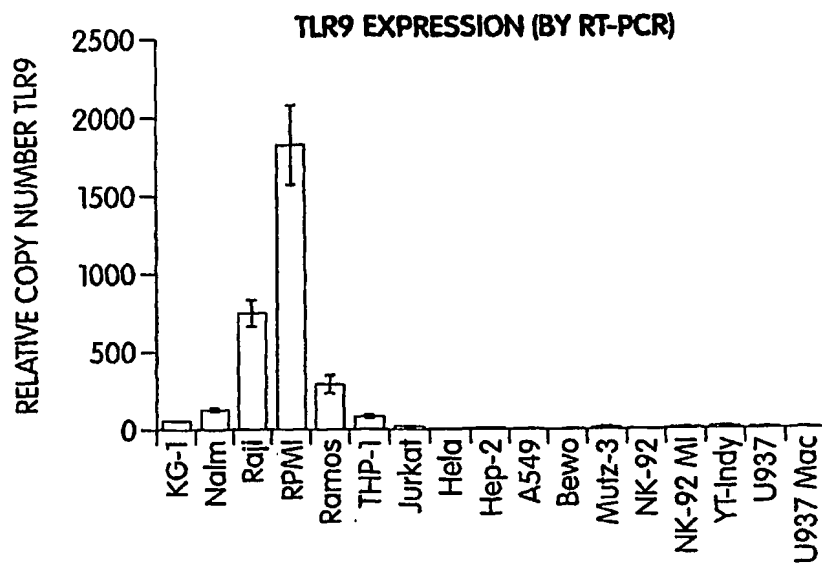


Fig. 10

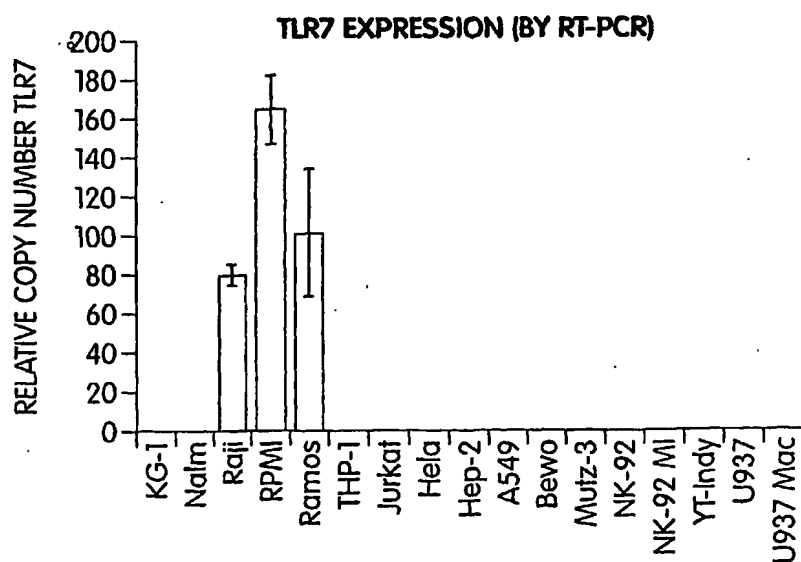


Fig. 11

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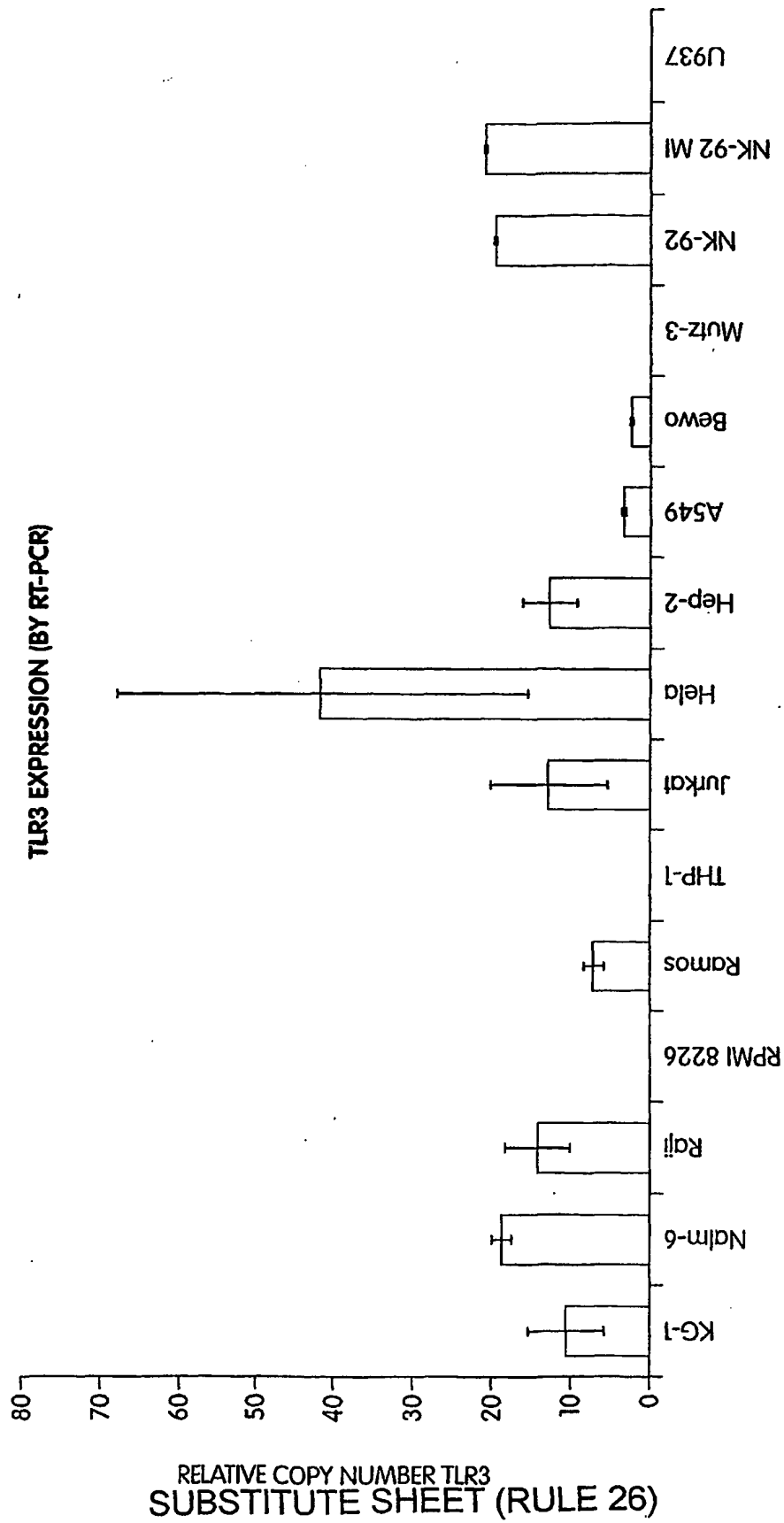


Fig. 12

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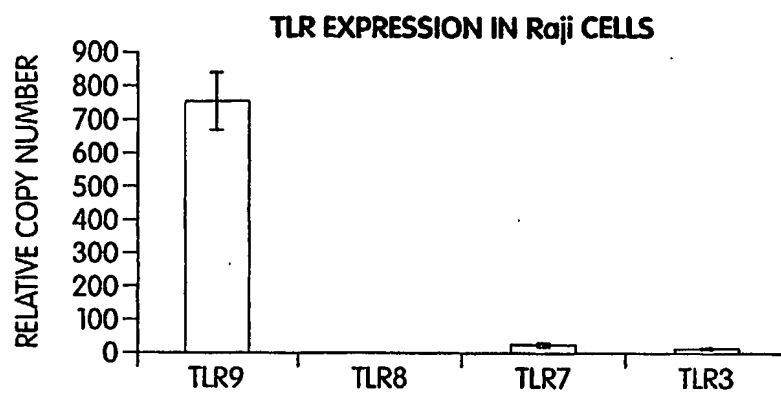


Fig. 13

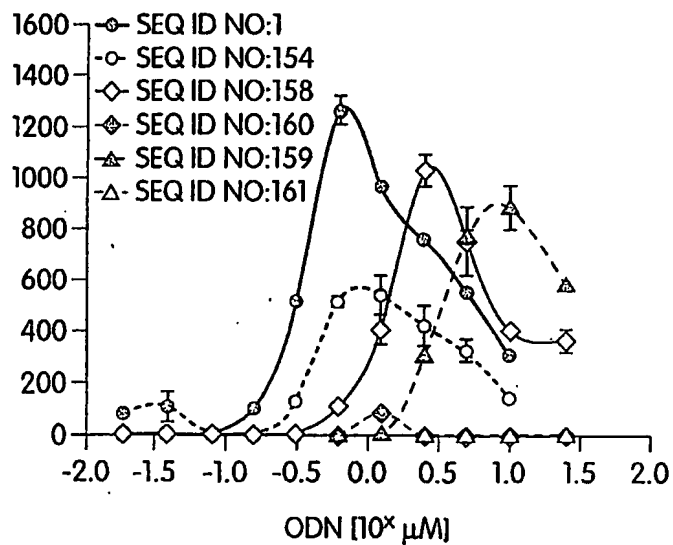


Fig. 14



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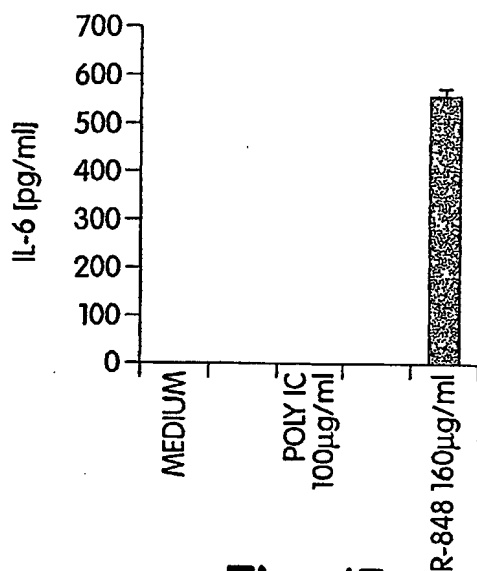


Fig. 15

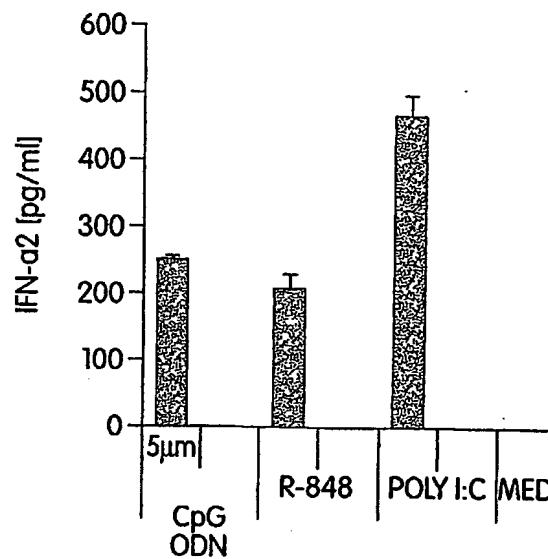
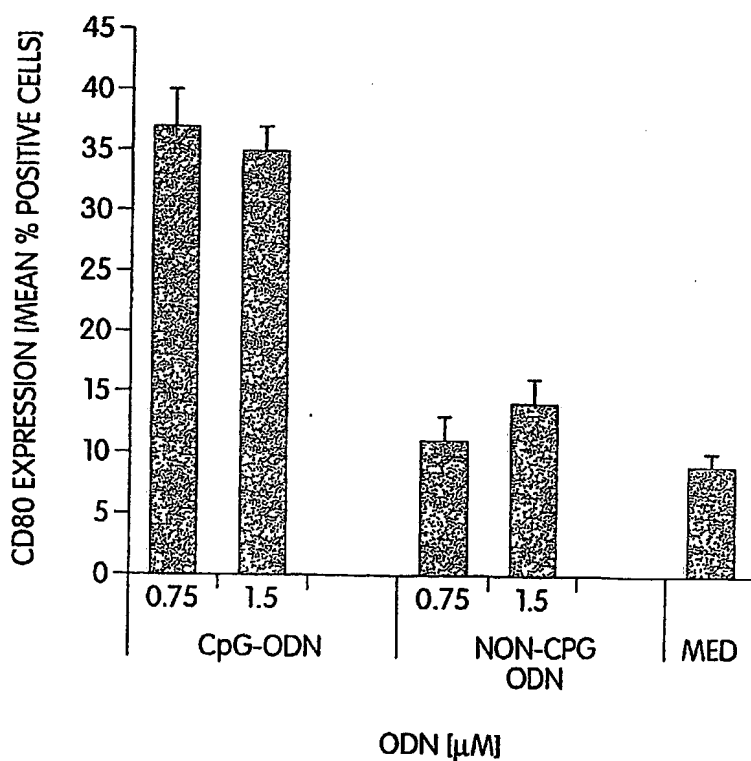


Fig. 16



ODN [µM]

Fig. 17

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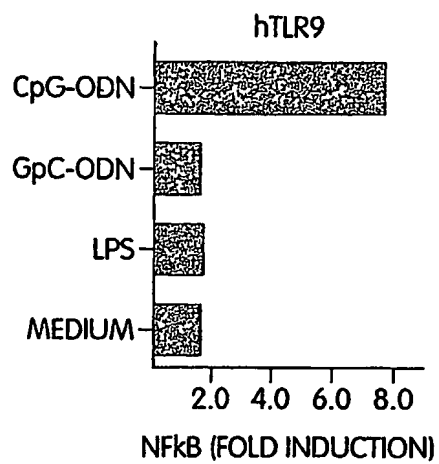


Fig. 18A

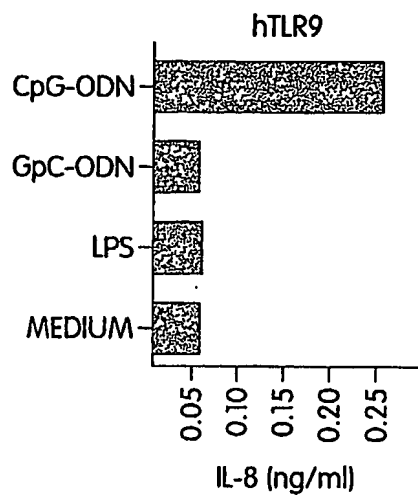


Fig. 18B

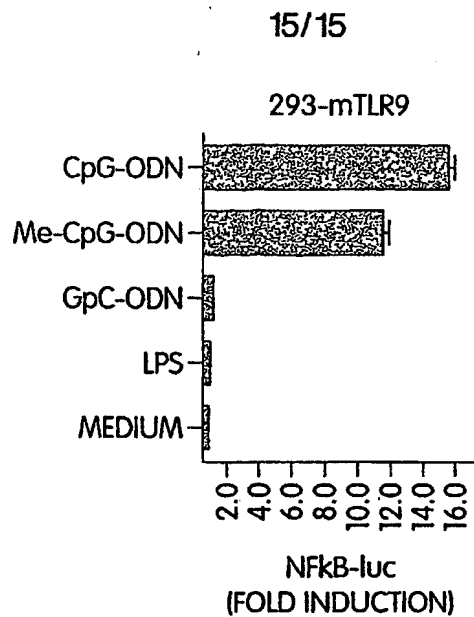


Fig. 19

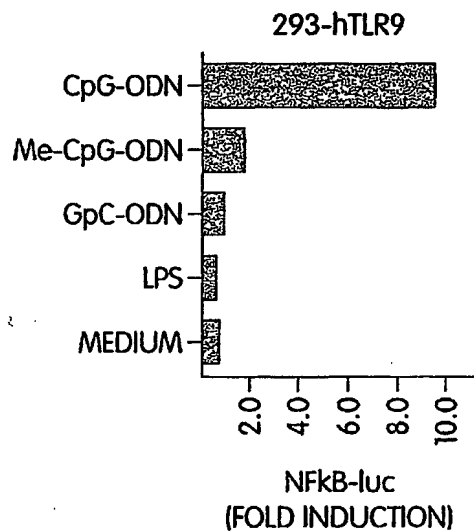
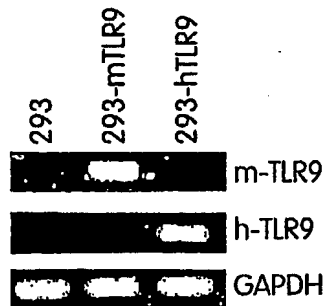


Fig. 20



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<110> COLEY PHARMACEUTICAL GmbH  
COLEY PHARMACEUTICAL GROUP INC.

<120> METHODS AND PRODUCTS FOR IDENTIFICATION AND ASSESSMENT OF TLR  
LIGANDS

<130> C1041.70024W000

<140> not yet assigned

<141> 2004-04-22

<150> US 60/464,586

<151> 2003-04-22

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 Thr Tyr Ile Ser Asn Ser Asp Leu Gln Arg Cys Val Asn Leu Gln Ala  
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 <213> Homo sapiens

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Phe Gly Met Leu Cys Ala Ser Ser Thr Thr Lys Cys Thr Val Ser His
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Glu Val Ala Asp Cys Ser His Leu Lys Leu Thr Gln Val Pro Asp Asp
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Leu Pro Thr Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu Arg
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Arg Leu Pro Ala Ala Asn Phe Thr Arg Tyr Ser Gln Leu Thr Ser Leu

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Gln Leu Ser Asp Lys Thr Phe Ala Phe Cys Thr Asn Leu Thr Glu Leu	115	120	125
His Leu Met Ser Asn Ser Ile Gln Lys Ile Lys Asn Asn Pro Phe Val	130	135	140
Lys Gln Lys Asn Leu Ile Thr Leu Asp Leu Ser His Asn Gly Leu Ser	145	150	155
Ser Thr Lys Leu Gly Thr Gln Val Gln Leu Glu Asn Leu Gln Glu Leu	165	170	175
Leu Leu Ser Asn Asn Lys Ile Gln Ala Leu Lys Ser Glu Glu Leu Asp	180	185	190
Ile Phe Ala Asn Ser Ser Leu Lys Lys Leu Glu Leu Ser Ser Asn Gln	195	200	205
Ile Lys Glu Phe Ser Pro Gly Cys Phe His Ala Ile Gly Arg Leu Phe	210	215	220
Gly Leu Phe Leu Asn Asn Val Gln Leu Gly Pro Ser Leu Thr Glu Lys	225	230	235
Leu Cys Leu Glu Leu Ala Asn Thr Ser Ile Arg Asn Leu Ser Leu Ser	245	250	255
Asn Ser Gln Leu Ser Thr Thr Ser Asn Thr Thr Phe Leu Gly Leu Lys	260	265	270
Trp Thr Asn Leu Thr Met Leu Asp Leu Ser Tyr Asn Asn Leu Asn Val	275	280	285
Val Gly Asn Asp Ser Phe Ala Trp Leu Pro Gln Leu Glu Tyr Phe Phe	290	295	300
Leu Glu Tyr Asn Asn Ile Gln His Leu Phe Ser His Ser Leu His Gly	305	310	315
Leu Phe Asn Val Arg Tyr Leu Asn Leu Lys Arg Ser Phe Thr Lys Gln	325	330	335
Ser Ile Ser Leu Ala Ser Leu Pro Lys Ile Asp Asp Phe Ser Phe Gln	340	345	350
Trp Leu Lys Cys Leu Glu His Leu Asn Met Glu Asp Asn Asp Ile Pro	355	360	365
Gly Ile Lys Ser Asn Met Phe Thr Gly Leu Ile Asn Leu Lys Tyr Leu	370	375	380
Ser Leu Ser Asn Ser Phe Thr Ser Leu Arg Thr Leu Thr Asn Glu Thr	385	390	395
Phe Val Ser Leu Ala His Ser Pro Leu His Ile Leu Asn Leu Thr Lys			400

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 Ser His Tyr Leu Cys Asn Thr Pro Pro His Tyr His Gly Phe Pro Val  
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 Ser Val His Arg Val Leu Gly Phe Lys Glu Ile Asp Arg Gln Thr Glu



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 Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Lys Arg Phe Lys Val  
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 His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile Ile  
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 Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu  
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 Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro  
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Tyr Asn Val Ala Asp Cys Ser His Leu Lys Leu Thr His Ile Pro Asp
35          40          45

Asp Leu Pro Ser Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu
50          55          60

Arg Arg Leu Pro Pro Thr Asn Phe Thr Arg Tyr Ser Gln Leu Ala Ile
65          70          75          80

Leu Asp Ala Gly Phe Asn Ser Ile Ser Lys Leu Glu Pro Glu Leu Cys
85          90          95

Gln Ile Leu Pro Leu Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu
100         105         110

Ser Gln Ile Ser Asp Gln Thr Phe Val Phe Cys Thr Asn Leu Thr Glu
115         120         125

Leu Asp Leu Met Ser Asn Ser Ile His Lys Ile Lys Ser Asn Pro Phe
130         135         140

Lys Asn Gln Lys Asn Leu Ile Lys Leu Asp Leu Ser His Asn Gly Leu
145         150         155         160

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 225 230 235 240  
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 450 455 460  
 Ser Tyr Asn Lys Tyr Leu Gln Leu Ser Thr Ser Ser Phe Ala Leu Val  
 465 470 475 480  
 Pro Ser Leu Gln Arg Leu Met Leu Arg Arg Val Ala Leu Lys Asn Val

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Asp	Leu	Ser	Asn	Asn	Asn	Ile	Ala	Asn	Ile	Asn	Glu	Asp	Leu	Leu	Glu			
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Gly	Leu	Glu	Asn	Leu	Glu	Ile	Leu	Asp	Phe	Gln	His	Asn	Asn	Leu	Ala			
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Arg	Leu	Trp	Lys	Arg	Ala	Asn	Pro	Gly	Gly	Pro	Val	Asn	Phe	Leu	Lys			
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Glu	Ile	Pro	Val	Gly	Val	Phe	Lys	Asn	Leu	Phe	Glu	Leu	Lys	Ser	Ile			
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Asn	Leu	Gly	Leu	Asn	Asn	Leu	Asn	Lys	Leu	Glu	Pro	Phe	Ile	Phe	Asp			
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Ser	Val	Glu	Lys	Asp	Val	Phe	Gly	Pro	Pro	Phe	Gln	Asn	Leu	Asn	Ser			
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Ser	Thr	His	Tyr	Leu	Cys	Asn	Thr	Pro	His	His	Tyr	Tyr	Gly	Phe	Pro			
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<210> 15
<211> 3934
<212> DNA
<213> Homo sapiens

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cgcgctggc tgggactctg atcccagcca tggccttcct ctctgcgtg agaccagaaa 240
gctgggagcc ctgctgggag acttggccct aaaccacaca gaagagctgg catgaaaccc 300
agagctttca gactccggag cctcagccct tcaccccgat tccattgctt cttgctaaat 360
gctgccgttt tatcacggag gtggttccta atattactta tcaatgcatg gagctgaatt 420
tctacaaaat ccccgacaac ctccccttct caaccaagaa cctggacctg agctttaatc 480
ccctgaggca tttaggcagc tatagcttct tcagtttccc agaactgcag gtgctggatt 540
tatccaggtg tgaaatccag acaattgaag atggggcata tcagagccta agccacctct 600
ctaccttaat attgacagga aaccccatcc agagttagc cctgggagcc ttttctggac 660
tatcaagttt acagaagctg gtggctgtgg agacaaatct agcatctcta gagaacttcc 720
ccattggaca tctcaaaact ttgaaagaac ttaatgtggc tcacaatctt atccaatctt 780
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acaagattca aagtatttat tgcacagact tgccgggttct acatcaaag cccctactca 900
atctctcttt agacctgtcc ctgaacccta tgaactttat ccaaccaggt gcatttaag 960

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&lt;210&gt; 16

&lt;211&gt; 839

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 16

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Met Met Ser Ala Ser Arg Leu Ala Gly Thr Leu Ile Pro Ala Met Ala
1           5           10           15

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```

Phe Leu Ser Cys Val Arg Pro Glu Ser Trp Glu Pro Cys Val Glu Val
20           25           30

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```

Val Pro Asn Ile Thr Tyr Gln Cys Met Glu Leu Asn Phe Tyr Lys Ile
35           40           45

```

```

Pro Asp Asn Leu Pro Phe Ser Thr Lys Asn Leu Asp Leu Ser Phe Asn
50           55           60

```

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Pro Leu Arg His Leu Gly Ser Tyr Ser Phe Phe Ser Phe Pro Glu Leu
65           70           75           80

```

```

Gln Val Leu Asp Leu Ser Arg Cys Glu Ile Gln Thr Ile Glu Asp Gly
85           90           95

```



Ala Tyr Gln Ser Leu Ser His Leu Ser Thr Leu Ile Leu Thr Gly Asn  
 100 105 110  
 Pro Ile Gln Ser Leu Ala Leu Gly Ala Phe Ser Gly Leu Ser Ser Leu  
 115 120 125  
 Gln Lys Leu Val Ala Val Glu Thr Asn Leu Ala Ser Leu Glu Asn Phe  
 130 135 140  
 Pro Ile Gly His Leu Lys Thr Leu Lys Glu Leu Asn Val Ala His Asn  
 145 150 155 160  
 Leu Ile Gln Ser Phe Lys Leu Pro Glu Tyr Phe Ser Asn Leu Thr Asn  
 165 170 175  
 Leu Glu His Leu Asp Leu Ser Ser Asn Lys Ile Gln Ser Ile Tyr Cys  
 180 185 190  
 Thr Asp Leu Arg Val Leu His Gln Met Pro Leu Leu Asn Leu Ser Leu  
 195 200 205  
 Asp Leu Ser Leu Asn Pro Met Asn Phe Ile Gln Pro Gly Ala Phe Lys  
 210 215 220  
 Glu Ile Arg Leu His Lys Leu Thr Leu Arg Asn Asn Phe Asp Ser Leu  
 225 230 235 240  
 Asn Val Met Lys Thr Cys Ile Gln Gly Leu Ala Gly Leu Glu Val His  
 245 250 255  
 Arg Leu Val Leu Gly Glu Phe Arg Asn Glu Gly Asn Leu Glu Lys Phe  
 260 265 270  
 Asp Lys Ser Ala Leu Glu Gly Leu Cys Asn Leu Thr Ile Glu Glu Phe  
 275 280 285  
 Arg Leu Ala Tyr Leu Asp Tyr Tyr Leu Asp Asp Ile Ile Asp Leu Phe  
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 Asn Cys Leu Thr Asn Val Ser Ser Phe Ser Leu Val Ser Val Thr Ile  
 305 310 315 320  
 Glu Arg Val Lys Asp Phe Ser Tyr Asn Phe Gly Trp Gln His Leu Glu  
 325 330 335  
 Leu Val Asn Cys Lys Phe Gly Gln Phe Pro Thr Leu Lys Leu Lys Ser  
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 Leu Lys Arg Leu Thr Phe Thr Ser Asn Lys Gly Gly Asn Ala Phe Ser  
 355 360 365  
 Glu Val Asp Leu Pro Ser Leu Glu Phe Leu Asp Leu Ser Arg Asn Gly  
 370 375 380  
 Leu Ser Phe Lys Gly Cys Cys Ser Gln Ser Asp Phe Gly Thr Thr Ser  
 385 390 395 400  
 Leu Lys Tyr Leu Asp Leu Ser Phe Asn Gly Val Ile Thr Met Ser Ser  
 405 410 415  
 Asn Phe Leu Gly Leu Glu Gln Leu Glu His Leu Asp Phe Gln His Ser

				420					425					430		
Asn	Leu	Lys	Gln	Met	Ser	Glu	Phe	Ser	Val	Phe	Leu	Ser	Leu	Arg	Asn	
		435					440					445				
Leu	Ile	Tyr	Leu	Asp	Ile	Ser	His	Thr	His	Thr	Arg	Val	Ala	Phe	Asn	
	450					455					460					
Gly	Ile	Phe	Asn	Gly	Leu	Ser	Ser	Leu	Glu	Val	Leu	Lys	Met	Ala	Gly	
465					470					475					480	
Asn	Ser	Phe	Gln	Glu	Asn	Phe	Leu	Pro	Asp	Ile	Phe	Thr	Glu	Leu	Arg	
				485					490					495		
Asn	Leu	Thr	Phe	Leu	Asp	Leu	Ser	Gln	Cys	Gln	Leu	Glu	Gln	Leu	Ser	
			500					505					510			
Pro	Thr	Ala	Phe	Asn	Ser	Leu	Ser	Ser	Leu	Gln	Val	Leu	Asn	Met	Ser	
		515					520					525				
His	Asn	Asn	Phe	Phe	Ser	Leu	Asp	Thr	Phe	Pro	Tyr	Lys	Cys	Leu	Asn	
	530					535					540					
Ser	Leu	Gln	Val	Leu	Asp	Tyr	Ser	Leu	Asn	His	Ile	Met	Thr	Ser	Lys	
545					550					555					560	
Lys	Gln	Glu	Leu	Gln	His	Phe	Pro	Ser	Ser	Leu	Ala	Phe	Leu	Asn	Leu	
				565					570					575		
Thr	Gln	Asn	Asp	Phe	Ala	Cys	Thr	Cys	Glu	His	Gln	Ser	Phe	Leu	Gln	
			580					585					590			
Trp	Ile	Lys	Asp	Gln	Arg	Gln	Leu	Val	Glu	Val	Glu	Arg	Met	Glu		
		595				600					605					
Cys	Ala	Thr	Pro	Ser	Asp	Lys	Gln	Gly	Met	Pro	Val	Leu	Ser	Leu	Asn	
	610					615					620					
Ile	Thr	Cys	Gln	Met	Asn	Lys	Thr	Ile	Ile	Gly	Val	Ser	Val	Leu	Ser	
625					630					635					640	
Val	Leu	Val	Val	Ser	Val	Val	Ala	Val	Leu	Val	Tyr	Lys	Phe	Tyr	Phe	
				645					650					655		
His	Leu	Met	Leu	Leu	Ala	Gly	Cys	Ile	Lys	Tyr	Gly	Arg	Gly	Glu	Asn	
			660					665					670			
Ile	Tyr	Asp	Ala	Phe	Val	Ile	Tyr	Ser	Ser	Gln	Asp	Glu	Asp	Trp	Val	
	675					680						685				
Arg	Asn	Glu	Leu	Val	Lys	Asn	Leu	Glu	Glu	Gly	Val	Pro	Pro	Phe	Gln	
	690					695					700					
Leu	Cys	Leu	His	Tyr	Arg	Asp	Phe	Ile	Pro	Gly	Val	Ala	Ile	Ala	Ala	
705					710					715					720	
Asn	Ile	Ile	His	Glu	Gly	Phe	His	Lys	Ser	Arg	Lys	Val	Ile	Val	Val	
			725					730						735		
Val	Ser	Gln	His	Phe	Ile	Gln	Ser	Arg	Trp	Cys	Ile	Phe	Glu	Tyr	Glu	
			740					745					750			
Ile	Ala	Gln	Thr	Trp	Gln	Phe	Leu	Ser	Ser	Arg	Ala	Gly	Ile	Ile	Phe	

755                      760                      765  
 Ile Val Leu Gln Lys Val Glu Lys Thr Leu Leu Arg Gln Gln Val Glu  
 770                      775                      780  
 Leu Tyr Arg Leu Leu Ser Arg Asn Thr Tyr Leu Glu Trp Glu Asp Ser  
 785                      790                      795                      800  
 Val Leu Gly Arg His Ile Phe Trp Arg Arg Leu Arg Lys Ala Leu Leu  
 805                      810                      815  
 Asp Gly Lys Ser Trp Asn Pro Glu Gly Thr Val Gly Thr Gly Cys Asn  
 820                      825                      830  
 Trp Gln Glu Ala Thr Ser Ile  
 835

<210> 17  
 <211> 782  
 <212> PRT  
 <213> Homo sapiens

<400> 17

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 20                      25                      30  
 Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu Ser  
 35                      40                      45  
 Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly Ala  
 50                      55                      60  
 Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr Asn  
 65                      70                      75                      80  
 Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu Lys  
 85                      90                      95  
 Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe Lys Leu Pro Glu  
 100                      105                      110  
 Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp Leu Ser Ser Asn  
 115                      120                      125  
 Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val Leu His Gln Met  
 130                      135                      140  
 Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn Phe  
 145                      150                      155                      160  
 Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr Leu  
 165                      170                      175  
 Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln Gly  
 180                      185                      190  
 Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg Asn  
 195                      200                      205

Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu Cys  
 210 215 220  
 Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr Leu  
 225 230 235 240  
 Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser Phe  
 245 250 255  
 Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr Asn  
 260 265 270  
 Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln Phe  
 275 280 285  
 Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser Asn  
 290 295 300  
 Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu Phe  
 305 310 315 320  
 Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser Gln  
 325 330 335  
 Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe Asn  
 340 345 350  
 Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu Glu  
 355 360 365  
 His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe Ser  
 370 375 380  
 Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His Thr  
 385 390 395 400  
 His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser Leu  
 405 410 415  
 Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu Pro  
 420 425 430  
 Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser Gln  
 435 440 445  
 Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser Ser  
 450 455 460  
 Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp Thr  
 465 470 475 480  
 Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser Leu  
 485 490 495  
 Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro Ser  
 500 505 510  
 Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr Cys  
 515 520 525  
 Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu Leu

530                      535                      540  
 Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln Gly  
 545                      550                      555                      560  
 Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr Ile  
                     565                      570                      575  
 Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala Val  
                     580                      585                      590  
 Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu Ala Gly Cys Ile  
                     595                      600                      605  
 Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr Ser  
                     610                      615                      620  
 Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu Glu  
 625                      630                      635                      640  
 Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe Ile  
                     645                      650                      655  
 Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His Lys  
                     660                      665                      670  
 Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser Arg  
                     675                      680                      685  
 Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu Ser  
                     690                      695                      700  
 Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys Thr  
 705                      710                      715                      720  
 Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn Thr  
                     725                      730                      735  
 Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp Arg  
                     740                      745                      750  
 Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu Gly  
                     755                      760                      765  
 Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile  
                     770                      775                      780

<210> 18  
 <211> 799  
 <212> PRT  
 <213> Homo sapiens

<400> 18

Met Glu Leu Asn Phe Tyr Lys Ile Pro Asp Asn Leu Pro Phe Ser Thr  
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 Lys Asn Leu Asp Leu Ser Phe Asn Pro Leu Arg His Leu Gly Ser Tyr  
                     20                      25                      30  
 Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu Ser Arg Cys  
                     35                      40                      45

Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu  
 50 55 60  
 Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly  
 65 70 75 80  
 Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr  
 85 90 95  
 Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu  
 100 105 110  
 Lys Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe Lys Leu Pro  
 115 120 125  
 Glu Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp Leu Ser Ser  
 130 135 140  
 Asn Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val Leu His Gln  
 145 150 155 160  
 Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn  
 165 170 175  
 Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr  
 180 185 190  
 Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln  
 195 200 205  
 Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg  
 210 215 220  
 Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu  
 225 230 235 240  
 Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr  
 245 250 255  
 Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser  
 260 265 270  
 Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr  
 275 280 285  
 Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln  
 290 295 300  
 Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser  
 305 310 315 320  
 Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu  
 325 330 335  
 Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser  
 340 345 350  
 Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe  
 355 360 365  
 Asn Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu

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Thr His Thr Arg Val	Ala Phe Asn Gly Ile Phe	Asn Gly Leu Ser Ser
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Pro Asp Ile Phe Thr	Glu Leu Arg Asn Leu Thr	Phe Leu Asp Leu Ser
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 Val His Val Asp Leu Ser Tyr Asn Tyr Ile Gln Thr Ile Thr Val Asn  
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 Asp Leu Gln Phe Leu Arg Glu Asn Pro Gln Val Asn Leu Ser Leu Asp  
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 Met Ser Leu Asn Pro Ile Asp Phe Ile Gln Asp Gln Ala Phe Gln Gly  
 210 215 220  
 Ile Lys Leu His Glu Leu Thr Leu Arg Gly Asn Phe Asn Ser Ser Asn  
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 Lys Arg Val Thr Glu Phe Ser Ala Phe Leu Ser Leu Glu Lys Leu Leu  
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 Tyr Leu Asp Ile Ser Tyr Thr Asn Thr Lys Ile Asp Phe Asp Gly Ile  
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 Trp His Gly Leu His His Leu Ser Asn Leu Ile Leu Thr Gly Asn Pro  
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&lt;213&gt; Homo sapiens

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 <213> Homo sapiens

<400> 26

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Glu Arg Leu Leu Leu Ser Phe Asn Tyr Ile Arg Thr Val Thr Ala Ser
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Ser Phe Pro Phe Leu Glu Gln Leu Gln Leu Leu Glu Leu Gly Ser Gln
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Tyr Thr Pro Leu Thr Ile Asp Lys Glu Ala Phe Arg Asn Leu Pro Asn
85          90          95

Leu Arg Ile Leu Asp Leu Gly Ser Ser Lys Ile Tyr Phe Leu His Pro
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Cys Gly Leu Ser Asp Ala Val Leu Lys Asp Gly Tyr Phe Arg Asn Leu

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 Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp Asn Ser Arg  
                                  740                      745                      750  
  
 Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp Gly Trp Cys  
                                  755                      760                      765  
  
 Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser Asp Leu Asn  
                                  770                      775                      780  
  
 Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln Tyr Gln Leu  
 785                                   790                      795                      800  
  
 Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln Gln Tyr Leu

805 810 815  
 Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu His Lys Leu  
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 Ser Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys Asp Asn Asn  
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 Ile Pro Leu Gln Thr Val Ala Thr Ile Ser  
 850 855

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 <213> Homo sapiens

<400> 27

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 Tyr Arg Phe Cys Asn Leu Thr Gln Val Pro Gln Val Leu Asn Thr Thr  
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 Glu Arg Leu Leu Leu Ser Phe Asn Tyr Ile Arg Thr Val Thr Ala Ser  
 50 55 60  
 Ser Phe Pro Phe Leu Glu Gln Leu Gln Leu Leu Glu Leu Gly Ser Gln  
 65 70 75 80  
 Tyr Thr Pro Leu Thr Ile Asp Lys Glu Ala Phe Arg Asn Leu Pro Asn  
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 Leu Arg Ile Leu Asp Leu Gly Ser Ser Lys Ile Tyr Phe Leu His Pro  
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 Asp Ala Phe Gln Gly Leu Phe His Leu Phe Glu Leu Arg Leu Tyr Phe  
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 Lys Ala Leu Thr Arg Leu Asp Leu Ser Lys Asn Gln Ile Arg Ser Leu  
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 Tyr Leu His Pro Ser Phe Gly Lys Leu Asn Ser Leu Lys Ser Ile Asp  
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 Phe Ser Ser Asn Gln Ile Phe Leu Val Cys Glu His Glu Leu Glu Pro  
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 Leu Gln Gly Lys Thr Leu Ser Phe Phe Ser Leu Ala Ala Asn Ser Leu  
 195 200 205  
 Tyr Ser Arg Val Ser Val Asp Trp Gly Lys Cys Met Asn Pro Phe Arg  
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 225 230 235 240

Asp Ile Thr Gly Asn Phe Ser Asn Ala Ile Ser Lys Ser Gln Ala Phe  
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 Ser Val Arg His Leu Asp Leu Ser His Gly Phe Val Phe Ser Leu Asn  
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 Ser Arg Val Phe Glu Thr Leu Lys Asp Leu Lys Val Leu Asn Leu Ala  
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 Asn Arg Leu Glu Asn Leu Asp Ile Leu Tyr Phe Leu Leu Arg Val Pro  
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 His Leu Gln Ile Leu Ile Leu Asn Gln Asn Arg Phe Ser Ser Cys Ser  
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 Arg Gly Leu Ser Leu Asn Ser Asn Arg Leu Thr Val Leu Ser His Asn  
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 Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln Gln Tyr Leu  
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 Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu His Lys Leu  
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&lt;210&gt; 28

&lt;211&gt; 365

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 28

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 Ser His Asn Asp Leu Pro Ala Asn Leu Glu Ile Leu Asp Ile Ser Arg  
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 Asn Gln Leu Leu Ala Pro Asn Pro Asp Val Phe Val Ser Leu Ser Val  
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<400> 30

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Phe	Arg	Gly	Cys	Asn	Leu	Thr	Gln	Ile	Pro	Trp	Ile	Leu	Asn	Thr	Thr
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Thr	Glu	Arg	Leu	Leu	Leu	Ser	Phe	Asn	Tyr	Ile	Ser	Met	Val	Val	Ala
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Thr	Ser	Phe	Pro	Leu	Leu	Glu	Arg	Leu	Gln	Leu	Leu	Glu	Leu	Gly	Thr
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Gln	Tyr	Ala	Asn	Leu	Thr	Ile	Gly	Pro	Gly	Ala	Phe	Arg	Asn	Leu	Pro
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Asn	Leu	Arg	Ile	Leu	Asp	Leu	Gly	Gln	Ser	Gln	Ile	Glu	Val	Leu	Asn
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 Ser Cys Gly Leu Ser Ser Ala Val Leu Ser Asp Gly Tyr Phe Arg Asn  
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 Arg Gly Val Arg Leu Glu Thr Leu Asp Leu Ser Glu Asn Gly Trp Thr  
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 Gln Arg Asn His Ile Gly Ile Ile Gln Asp Gln Thr Phe Arg Leu Leu  
 370 375 380  
 Lys Thr Leu Gln Thr Leu Asp Leu Arg Asp Asn Ala Leu Lys Ala Ile  
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 Gly Phe Ile Pro Ser Ile Gln Met Val Leu Leu Gly Gly Asn Lys Leu  
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 Val His Leu Pro His Ile His Phe Thr Ala Asn Phe Leu Glu Leu Ser  
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Leu Thr Glu Asn Met	Leu Gln Leu Ala Trp	Glu Thr Gly Leu Cys Trp
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Asp Val Phe Gln Gly	Leu Ser Arg Leu Gln Ile	Leu Tyr Leu Ser Asn
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Leu Leu Cys Pro Asp	Pro Ala Leu Phe Ser	Ser Leu Arg Val Leu Asp
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Ile Thr His Asn Glu	Phe Val Cys Asn Cys	Glu Leu Ser Thr Phe Ile
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Val Tyr Cys Met Tyr	Pro Asn Ser Leu Leu Gly	Gly Ser Leu Tyr Asn
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Ile Ser Thr Glu Asp	Cys Asp Glu Glu Glu	Ala Met Arg Ser Leu Lys
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Phe Ser Leu Phe Ile	Leu Cys Thr Val Thr	Leu Thr Leu Phe Leu Val
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Ile Thr Leu Val Val	Ile Lys Phe Arg Gly	Ile Cys Phe Leu Cys Tyr
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Lys Thr Ile Gln Lys	Leu Val Phe Lys Asp	Lys Val Trp Ser Leu Glu
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Phe Glu Trp Ala Gln	Asn Ala Leu Leu Lys	His Leu Asp Ala His Tyr
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Ser Ser Arg Asn Arg	Leu Arg Leu Cys Phe	Glu Glu Arg Asp Phe Ile
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Pro Gly Glu Asn His	Ile Ser Asn Ile Gln	Ala Ala Val Trp Gly Ser
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Arg Lys Thr Val Cys	Leu Val Ser Arg His	Phe Leu Lys Asp Gly Trp
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Cys Leu Glu Ala Phe	Arg Tyr Ala Gln	Ser Arg Ser Leu Ser Asp Leu

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	805	810 815
Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu Asp Lys		
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&lt;211&gt; 3373

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 31

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<213> Homo sapiens

<400> 32

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<211> 3418

<212> DNA

<213> Homo sapiens

<400> 33

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<210> 34

<211> 1049

<212> PRT

<213> Homo sapiens

<400> 34

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Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile  
35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro  
50 55 60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile  
65 70 75 80

Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe  
85 90 95

Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys  
100 105 110

Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr  
115 120 125

Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln  
130 135 140

Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile  
145 150 155 160

Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile  
165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser  
180 185 190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val  
195 200 205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro  
210 215 220

Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile  
225 230 235 240

Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu  
245 250 255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro

260 265 270  
 Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala  
 275 280 285  
 Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His  
 290 295 300  
 Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp  
 305 310 315 320  
 Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu  
 325 330 335  
 His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu  
 340 345 350  
 Leu Gln Val Tyr Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser  
 355 360 365  
 Leu Lys Ser Leu Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu  
 370 375 380  
 Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu  
 385 390 395 400  
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 405 410 415  
 Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys  
 420 425 430  
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 435 440 445  
 Arg Thr Ser Val Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His  
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 Tyr Phe Arg Tyr Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys  
 465 470 475 480  
 Glu Ala Ser Phe Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln  
 485 490 495  
 Thr Leu Asp Leu Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp  
 500 505 510  
 Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu  
 515 520 525  
 Ile Ser Gln Thr Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu  
 530 535 540  
 Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr  
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 Ala Phe Glu Glu Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn  
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 Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr  
 580 585 590  
 Lys Asn Leu Lys Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile

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 Ser Ser Ser Thr Ser Arg Thr Met Glu Ser Glu Ser Leu Arg Thr Leu  
 610 615 620  
 Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn  
 625 630 635 640  
 Arg Tyr Leu Gln Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp  
 645 650 655  
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 Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys  
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 Ser Phe Ser Trp Lys Lys Leu Gln Cys Leu Lys Asn Leu Glu Thr Leu  
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 725 730 735  
 Ser Leu Thr Lys Tyr Phe Leu Gln Asp Ala Phe Gln Leu Arg Tyr Leu  
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 Asp Leu Ser Ser Asn Lys Ile Gln Met Ile Gln Lys Thr Ser Phe Pro  
 755 760 765  
 Glu Asn Val Leu Asn Asn Leu Lys Met Leu Leu Leu His His Asn Arg  
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 Phe Leu Cys Thr Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His  
 785 790 795 800  
 Thr Glu Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly  
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 Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr  
 820 825 830  
 Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser  
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 Val Ser Leu Phe Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe  
 850 855 860  
 Trp Asp Val Trp Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly  
 865 870 875 880  
 Tyr Gln Arg Leu Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val  
 885 890 895  
 Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu  
 900 905 910  
 Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu  
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 Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser

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 Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys  
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 Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln  
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 Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu  
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 Lys Pro Phe Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys  
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 Gly Ser Ser Val Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro  
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 Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Ala Thr Asp Asn His  
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<210> 35  
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<400> 35

Met Val Phe Pro Met Trp Thr Leu Lys Arg Gln Ile Leu Ile Leu Phe  
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 Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro  
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 Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile  
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 Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe  
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 Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys  
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 Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr  
                          115                      120                      125  
 Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln  
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 Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile  
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 Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile  
                          165                      170                      175

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 Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile  
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 Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro  
 260 265 270  
 Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala  
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 370 375 380  
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 Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys  
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 Ile Ser Pro Ser Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala  
 435 440 445  
 Arg Thr Ser Val Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His  
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 Tyr Phe Arg Tyr Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys  
 465 470 475 480  
 Glu Ala Ser Phe Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln  
 485 490 495  
 Thr Leu Asp Leu Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp

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 Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu  
 515 520 525  
 Ile Ser Gln Thr Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu  
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 Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr  
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 Ala Phe Glu Glu Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn  
 565 570 575  
 Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr  
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 Lys Asn Leu Lys Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile  
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 610 615 620  
 Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn  
 625 630 635 640  
 Arg Tyr Leu Gln Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp  
 645 650 655  
 Ile Ser Lys Asn Ser Leu Ser Phe Leu Pro Ser Gly Val Phe Asp Gly  
 660 665 670  
 Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys  
 675 680 685  
 Ser Phe Ser Trp Lys Lys Leu Gln Cys Leu Lys Asn Leu Glu Thr Leu  
 690 695 700  
 Asp Leu Ser His Asn Gln Leu Thr Thr Val Pro Glu Arg Leu Ser Asn  
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 Cys Ser Arg Ser His Lys Asn Leu Ile Leu Lys Asn Asn Gln Ile Arg  
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 Ser Pro Thr Lys Tyr Phe Leu Gln Asp Ala Phe Gln Leu Arg Tyr Leu  
 740 745 750  
 Asp Leu Ser Ser Asn Lys Ile Gln Met Ile Gln Lys Thr Ser Phe Pro  
 755 760 765  
 Glu Asn Val Leu Asn Asn Leu Lys Met Leu Leu Leu His His Asn Arg  
 770 775 780  
 Phe Leu Cys Thr Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His  
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 Thr Glu Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly  
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 Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr  
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 Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser

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 Trp Asp Val Trp Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly  
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 Tyr Gln Arg Leu Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val  
 885 890 895  
 Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu  
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 Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu  
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 Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser  
 930 935 940  
 Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys  
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 Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln  
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 Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu  
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 Gly Ser Ser Val Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro  
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 Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile  
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 Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro  
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Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe  
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 Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys  
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 Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln  
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 Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile  
 145 150 155 160  
 Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile  
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 Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser  
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 Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val  
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 Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro  
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 Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile  
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 Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu  
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 Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro  
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 Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala  
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 His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu  
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 Leu Lys Ser Leu Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu  
 370 375 380  
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 Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr  
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 Lys Asn Leu Lys Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile  
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 Arg Tyr Leu Gln Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp  
 645 650 655  
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 Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys  
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 Asp Leu Ser His Asn Gln Leu Thr Thr Val Pro Glu Arg Leu Ser Asn  
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 Cys Ser Arg Ser Leu Lys Asn Leu Ile Leu Lys Asn Asn Gln Ile Arg  
 725 730 735  
 Ser Leu Thr Lys Tyr Phe Leu Gln Asp Ala Phe Gln Leu Arg Tyr Leu

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              740              745              750
Asp Leu Ser Ser Asn Lys Ile Gln Met Ile Gln Lys Thr Ser Phe Pro
              755              760              765

Glu Asn Val Leu Asn Asn Leu Lys Met Leu Leu Leu His His Asn Arg
              770              775              780

Phe Leu Cys Thr Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His
785              790              795              800

Thr Glu Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly
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Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr
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Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser
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Val Ser Leu Phe Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe
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Trp Asp Val Trp Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly
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Tyr Gln Arg Leu Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val
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Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu
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Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu
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Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser
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Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys
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Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln
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Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu
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Lys Pro Phe Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys
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Gly Ser Ser Val Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro
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Val Ala Tyr Ser Gln Val Phe Lys Glu Thr Val
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&lt;213&gt; Homo sapiens

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Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile
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Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro
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Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile
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Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe
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Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
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Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr
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Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
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Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile
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Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
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Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
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Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val
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Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro
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Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile
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Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
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Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro
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Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
          275          280          285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
          290          295          300

Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp
          305          310          315          320

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Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu  
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 355 360 365  
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 370 375 380  
 Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu  
 385 390 395 400  
 Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met  
 405 410 415  
 Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys  
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 Ile Ser Pro Ser Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala  
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 Arg Thr Ser Val Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His  
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 Tyr Phe Arg Tyr Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys  
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 Glu Ala Ser Phe Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln  
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 Thr Leu Asp Leu Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp  
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 Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu  
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 Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr  
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 Ala Phe Glu Glu Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn  
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 Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr  
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 Lys Asn Leu Lys Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile  
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 Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn  
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 Arg Tyr Leu Gln Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp

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			660					665					670		
Met	Pro	Pro	Asn	Leu	Lys	Asn	Leu	Ser	Leu	Ala	Lys	Asn	Gly	Leu	Lys
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Ser	Phe	Ser	Trp	Lys	Lys	Leu	Gln	Cys	Leu	Lys	Asn	Leu	Glu	Thr	Leu
			690			695					700				
Asp	Leu	Ser	His	Asn	Gln	Leu	Thr	Thr	Val	Pro	Glu	Arg	Leu	Ser	Asn
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Cys	Ser	Arg	Ser	Leu	Lys	Asn	Leu	Ile	Leu	Lys	Asn	Asn	Gln	Ile	Arg
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Ser	Leu	Thr	Lys	Tyr	Phe	Leu	Gln	Asp	Ala	Phe	Gln	Leu	Arg	Tyr	Leu
			740					745					750		
Asp	Leu	Ser	Ser	Asn	Lys	Ile	Gln	Met	Ile	Gln	Lys	Thr	Ser	Phe	Pro
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Glu	Asn	Val	Leu	Asn	Asn	Leu	Lys	Met	Leu	Leu	Leu	His	His	Asn	Arg
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Phe	Leu	Cys	Thr	Cys	Asp	Ala	Val	Trp	Phe	Val	Trp	Trp	Val	Asn	His
785					790					795					800
Thr	Glu	Val	Thr	Ile	Pro	Tyr	Leu	Ala	Thr	Asp	Val	Thr	Cys	Val	Gly
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Pro	Gly	Ala	His	Lys	Gly	Gln	Ser	Val	Ile	Ser	Leu	Asp	Leu	Tyr	Thr
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Cys	Glu	Leu	Asp	Leu	Thr	Asn	Leu	Ile	Leu	Phe	Ser	Leu	Ser	Ile	Ser
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Val	Ser	Leu	Phe	Leu	Met	Val	Met	Met	Thr	Ala	Ser	His	Leu	Tyr	Phe
			850			855					860				
Trp	Asp	Val	Trp	Tyr	Ile	Tyr	His	Phe	Cys	Lys	Ala	Lys	Ile	Lys	Gly
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Tyr	Gln	Arg	Leu	Ile	Ser	Pro	Asp	Cys	Cys	Tyr	Asp	Ala	Phe	Ile	Val
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			900					905					910		
Val	Ala	Lys	Leu	Glu	Asp	Pro	Arg	Glu	Lys	His	Phe	Asn	Leu	Cys	Leu
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Glu	Glu	Arg	Asp	Trp	Leu	Pro	Gly	Gln	Pro	Val	Leu	Glu	Asn	Leu	Ser
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Tyr	Ala	Lys	Thr	Glu	Asn	Phe	Lys	Ile	Ala	Phe	Tyr	Leu	Ser	His	Gln
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Arg	Gln	Leu	Thr 740	Lys	Tyr	Phe	Leu	Glu 745	Asp	Ala	Leu	Gln	Leu 750	Arg	Tyr
Leu	Asp	Ile 755	Ser	Ser	Asn	Lys	Ile 760	Gln	Val	Ile	Gln	Lys 765	Thr	Ser	Phe
Pro	Glu	Asn	Val	Leu	Asn	Asn 775	Leu	Glu	Met	Leu	Val 780	Leu	His	His	Asn
Arg 785	Phe	Leu	Cys	Asn 790	Cys	Asp	Ala	Val	Trp	Phe 795	Val	Trp	Trp	Val	Asn 800
His	Thr	Asp	Val	Thr	Ile	Pro	Tyr	Leu	Ala	Thr	Asp	Val	Thr	Cys	Val

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 Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr  
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 Thr Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile  
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 Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe  
 850 855 860  
 Phe Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys  
 865 870 875 880  
 Gly Tyr Gln His Leu Gln Ser Met Glu Ser Cys Tyr Asp Ala Phe Ile  
 885 890 895  
 Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu  
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 Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His  
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 980 985 990  
 Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu  
 995 1000 1005  
 Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His  
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 Thr Leu Pro Cys Glu Val Lys Val Asn Ile Pro Glu Ala His Val Ile  
 35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro  
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 Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile  
 65 70 75 80  
 Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu  
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 Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys  
 100 105 110  
 Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp  
 115 120 125  
 Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln  
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 Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile  
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 Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr  
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 Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val  
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 Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro  
 210 215 220  
 Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile  
 225 230 235 240  
 Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp Leu  
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 Ser Gly Asn Cys Pro Arg Cys Tyr Asn Val Pro Tyr Pro Cys Thr Pro  
 260 265 270  
 Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn Ser  
 275 280 285  
 Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His  
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 Val Pro Pro Thr Trp Phe Lys Asn Met Arg Asn Leu Gln Glu Leu Asp  
 305 310 315 320  
 Leu Ser Gln Asn Tyr Leu Ala Arg Glu Ile Glu Glu Ala Lys Phe Leu  
 325 330 335  
 His Phe Leu Pro Asn Leu Val Glu Leu Asp Phe Ser Phe Asn Tyr Glu  
 340 345 350  
 Leu Gln Val Tyr His Ala Ser Ile Thr Leu Pro His Ser Leu Ser Ser  
 355 360 365  
 Leu Glu Asn Leu Lys Ile Leu Arg Val Lys Gly Tyr Val Phe Lys Glu

370 375 380  
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 385 390 395 400  
 Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asp Leu Asn Ile  
 405 410 415  
 Phe Lys His Phe Glu Asn Leu Lys Leu Ile Asp Leu Ser Val Asn Lys  
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 Ile Ser Pro Ser Glu Glu Ser Arg Glu Val Gly Phe Cys Pro Asn Ala  
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 Gln Thr Ser Val Asp Arg His Gly Pro Gln Val Leu Glu Ala Leu His  
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 Tyr Phe Arg Tyr Asp Glu Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys  
 465 470 475 480  
 Glu Pro Pro Ser Phe Leu Pro Leu Asn Ala Asp Cys His Ile Tyr Gly  
 485 490 495  
 Gln Thr Leu Asp Leu Ser Arg Asn Asn Ile Phe Phe Ile Lys Pro Ser  
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 Leu Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu Tyr Ser  
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 Thr Ala Phe Glu Glu Leu Gln Ser Leu Glu Val Leu Asp Leu Ser Ser  
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 Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe  
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 Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp  
 595 600 605  
 Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile  
 610 615 620  
 Leu Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Ala Gly Asp  
 625 630 635 640  
 Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu  
 645 650 655  
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 660 665 670  
 Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu  
 675 680 685  
 Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile  
 690 695 700  
 Leu Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala

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Arg	Gln	Leu	Thr	Lys	Tyr	Phe	Leu	Glu	Asp	Ala	Leu	Gln	Leu	Arg	Tyr				
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Leu	Asp	Ile	Ser	Ser	Asn	Lys	Ile	Gln	Val	Ile	Gln	Lys	Thr	Ser	Phe				
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Pro	Glu	Asn	Val	Leu	Asn	Asn	Leu	Glu	Met	Leu	Val	Leu	His	His	Asn				
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Arg	Phe	Leu	Cys	Asn	Cys	Asp	Ala	Val	Trp	Phe	Val	Trp	Trp	Val	Asn				
785					790					795					800				
His	Thr	Asp	Val	Thr	Ile	Pro	Tyr	Leu	Ala	Thr	Asp	Val	Thr	Cys	Val				
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Gly	Pro	Gly	Ala	His	Lys	Gly	Gln	Ser	Val	Ile	Ser	Leu	Asp	Leu	Tyr				
			820					825						830					
Thr	Cys	Glu	Leu	Asp	Leu	Thr	Asn	Leu	Ile	Leu	Phe	Ser	Val	Ser	Ile				
		835					840						845						
Ser	Ser	Val	Leu	Phe	Leu	Met	Val	Val	Met	Thr	Thr	Ser	His	Leu	Phe				
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Phe	Trp	Asp	Met	Trp	Tyr	Ile	Tyr	Tyr	Phe	Trp	Lys	Ala	Lys	Ile	Lys				
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Gly	Tyr	Gln	His	Leu	Gln	Ser	Met	Glu	Ser	Cys	Tyr	Asp	Ala	Phe	Ile				
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Val	Tyr	Asp	Thr	Lys	Asn	Ser	Ala	Val	Thr	Glu	Trp	Val	Leu	Gln	Glu				
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Leu	Val	Ala	Lys	Leu	Glu	Asp	Pro	Arg	Glu	Lys	His	Phe	Asn	Leu	Cys				
		915					920						925						
Leu	Glu	Glu	Arg	Asp	Trp	Leu	Pro	Gly	Gln	Pro	Val	Leu	Glu	Asn	Leu				
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Ser	Gln	Ser	Ile	Gln	Leu	Ser	Lys	Lys	Thr	Val	Phe	Val	Met	Thr	Gln				
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Lys	Tyr	Ala	Lys	Thr	Glu	Ser	Phe	Lys	Met	Ala	Phe	Tyr	Leu	Ser	His				
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Gln	Arg	Leu	Leu	Asp	Glu	Lys	Val	Asp	Val	Ile	Ile	Leu	Ile	Phe	Leu				
			980					985						990					
Glu	Lys	Pro	Leu	Gln	Lys	Ser	Lys	Phe	Leu	Gln	Leu	Arg	Lys	Arg	Leu				
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 Thr Leu Pro Cys Glu Val Lys Val Asn Ile Pro Glu Ala His Val Ile  
 35 40 45  
  
 Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro  
 50 55 60  
  
 Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile  
 65 70 75 80  
  
 Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu  
 85 90 95  
  
 Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys  
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 Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp  
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 Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln  
 130 135 140  
  
 Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile  
 145 150 155 160  
  
 Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr  
 165 170 175  
  
 Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Asn Val Ser  
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 Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val  
 195 200 205  
  
 Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro  
 210 215 220  
  
 Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile  
 225 230 235 240  
  
 Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp Leu  
 245 250 255  
  
 Ser Gly Asn Cys Pro Arg Cys Tyr Asn Val Pro Tyr Pro Cys Thr Pro  
 260 265 270  
  
 Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn Ser  
 275 280 285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His  
 290 295 300  
 Val Pro Pro Thr Trp Phe Lys Asn Met Arg Asn Leu Gln Glu Leu Asp  
 305 310 315 320  
 Leu Ser Gln Asn Tyr Leu Ala Arg Glu Ile Glu Glu Ala Lys Phe Leu  
 325 330 335  
 His Phe Leu Pro Asn Leu Val Glu Leu Asp Phe Ser Phe Asn Tyr Glu  
 340 345 350  
 Leu Gln Val Tyr His Ala Ser Ile Thr Leu Pro His Ser Leu Ser Ser  
 355 360 365  
 Leu Glu Asn Leu Lys Ile Leu Arg Val Lys Gly Tyr Val Phe Lys Glu  
 370 375 380  
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 385 390 395 400  
 Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asp Leu Asn Ile  
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 Phe Lys His Phe Glu Asn Leu Lys Leu Ile Asp Leu Ser Val Asn Lys  
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 Ile Ser Pro Ser Glu Glu Ser Arg Glu Val Gly Phe Cys Pro Asn Ala  
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 Gln Thr Ser Val Asp Arg His Gly Pro Gln Val Leu Glu Ala Leu His  
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 Tyr Phe Arg Tyr Asp Glu Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys  
 465 470 475 480  
 Glu Pro Pro Ser Phe Leu Pro Leu Asn Ala Asp Cys His Ile Tyr Gly  
 485 490 495  
 Gln Thr Leu Asp Leu Ser Arg Asn Asn Ile Phe Phe Ile Lys Pro Ser  
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 Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe  
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 Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp  
 595 600 605  
 Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile

610 615 620  
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 625 630 635 640  
 Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu  
 645 650 655  
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 Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu  
 675 680 685  
 Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile  
 690 695 700  
 Leu Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala  
 705 710 715 720  
 Asn Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile  
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 Arg Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr  
 740 745 750  
 Leu Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe  
 755 760 765  
 Pro Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn  
 770 775 780  
 Arg Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn  
 785 790 795 800  
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 Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr  
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 Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe  
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 Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu  
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 Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu  
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 Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln



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 Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu  
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 Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His  
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 Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn  
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 Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro  
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 Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile  
 65                      70                      75                      80  
  
 Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu  
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 Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys  
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 Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp  
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 Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln  
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 Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile  
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 Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr  
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 Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Asn Val Ser  
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Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val  
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 Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro  
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 Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile  
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 Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp Leu  
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 Ser Gly Asn Cys Pro Arg Cys Tyr Asn Val Pro Tyr Pro Cys Thr Pro  
 260 265 270  
 Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn Ser  
 275 280 285  
 Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His  
 290 295 300  
 Val Pro Pro Thr Trp Phe Lys Asn Met Arg Asn Leu Gln Glu Leu Asp  
 305 310 315 320  
 Leu Ser Gln Asn Tyr Leu Ala Arg Glu Ile Glu Glu Ala Lys Phe Leu  
 325 330 335  
 His Phe Leu Pro Asn Leu Val Glu Leu Asp Phe Ser Phe Asn Tyr Glu  
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 Leu Gln Val Tyr His Ala Ser Ile Thr Leu Pro His Ser Leu Ser Ser  
 355 360 365  
 Leu Glu Asn Leu Lys Ile Leu Arg Val Lys Gly Tyr Val Phe Lys Glu  
 370 375 380  
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 385 390 395 400  
 Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asp Leu Asn Ile  
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 Phe Lys His Phe Glu Asn Leu Lys Leu Ile Asp Leu Ser Val Asn Lys  
 420 425 430  
 Ile Ser Pro Ser Glu Glu Ser Arg Glu Val Gly Phe Cys Pro Asn Ala  
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 Gln Thr Ser Val Asp Arg His Gly Pro Gln Val Leu Glu Ala Leu His  
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 Tyr Phe Arg Tyr Asp Glu Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys  
 465 470 475 480  
 Glu Pro Pro Ser Phe Leu Pro Leu Asn Ala Asp Cys His Ile Tyr Gly  
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 Thr Ala Phe Glu Glu Leu Gln Ser Leu Glu Val Leu Asp Leu Ser Ser  
 565                      570                      575  
 Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe  
 580                      585                      590  
 Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp  
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 Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile  
 610                      615                      620  
 Leu Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Ala Gly Asp  
 625                      630                      635                      640  
 Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu  
 645                      650                      655  
 Asp Ile Ser Arg Asn Ser Leu Asn Ser Leu Pro Pro Glu Val Phe Glu  
 660                      665                      670  
 Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu  
 675                      680                      685  
 Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile  
 690                      695                      700  
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 705                      710                      715                      720  
 Asn Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile  
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 Arg Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr  
 740                      745                      750  
 Leu Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe  
 755                      760                      765  
 Pro Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn  
 770                      775                      780  
 Arg Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn  
 785                      790                      795                      800  
 His Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val  
 805                      810                      815  
 Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr  
 820                      825                      830  
 Thr Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile  
 835                      840                      845  
 Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe

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 Phe Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys  
 865                      870                      875                      880  
 Gly Tyr Gln His Leu Gln Ser Met Glu Ser Cys Tyr Asp Ala Phe Ile  
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 Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu  
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 Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys  
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 Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu  
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 Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln  
 945                      950                      955                      960  
 Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His  
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 Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu  
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 Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu  
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 Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His  
                                  1010                      1015                      1020  
 Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn  
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 His Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val  
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ccacaacaac atttatactt taacagataa gtataacctg gaaagcaagt ccctggtaga	2040

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attagttttc agtggcaatc gccttgacat tttgtggaat gatgatgaca acaggtatat 2100
ctccattttc aaaggtctca agaatctgac acgtctggat ttatccctta ataggctgaa 2160
gcacatccca aatgaagcat tccttaatct gccagcgagt ctactgaac tacatataaa 2220
tgataaatatg ttaaagtttt ttaactggac attactccag cagtttcctc gtctcgagtt 2280
gcttgactta cgtggaaaca aactactctt ttttaactgat agcctatctg actttacatc 2340
ttcccttcgg aactgctgc tgagtcataa caggatttcc cacctaccct ctggctttct 2400
ttctgaagtc agtagtctga agcacctcga ttttaagttcc aatctgctaa aaacaatcaa 2460
caaatccgca cttgaaacta agaccaccac caaattatct atgttggaac tacacggaaa 2520
cccctttgaa tgcacctgtg acattggaga tttccgaaga tggatggatg aacatctgaa 2580
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tatgtatgtc gattccatta agcaatacta actgacgtta agtcattgatt tcgcgccata 3360
ataaagatgc aaaggaatga ctttctgtg ttagttatct attgctatgt aacaaattat 3420
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&lt;210&gt; 50

&lt;211&gt; 1041

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 50

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Met Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile Phe Leu
1           5           10           15

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Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe Ser Arg
20           25           30

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Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu  
 35 40 45  
 Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr  
 50 55 60  
 Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn  
 65 70 75 80  
 Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His  
 85 90 95  
 Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn  
 100 105 110  
 Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg  
 115 120 125  
 Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu  
 130 135 140  
 Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile Tyr Asn  
 145 150 155 160  
 Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr  
 165 170 175  
 Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile  
 180 185 190  
 Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu  
 195 200 205  
 Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu  
 210 215 220  
 Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu  
 225 230 235 240  
 Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn  
 245 250 255  
 Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly  
 260 265 270  
 Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln  
 275 280 285  
 Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala  
 290 295 300  
 Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe  
 305 310 315 320  
 Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu  
 325 330 335  
 Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser  
 340 345 350  
 Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser

355 360 365  
 Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu  
 370 375 380  
 Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn  
 385 390 395 400  
 Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn  
 405 410 415  
 Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro  
 420 425 430  
 Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln  
 435 440 445  
 Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His  
 450 455 460  
 Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala  
 465 470 475 480  
 Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile  
 485 490 495  
 Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu Asn Leu  
 500 505 510  
 Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe Ser Ala  
 515 520 525  
 Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu Asp Phe  
 530 535 540  
 Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val Leu Asp  
 545 550 555 560  
 Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr His His  
 565 570 575  
 Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn Leu Ser  
 580 585 590  
 His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu Ser Lys  
 595 600 605  
 Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp  
 610 615 620  
 Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu Lys Asn  
 625 630 635 640  
 Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn  
 645 650 655  
 Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His Ile Asn  
 660 665 670  
 Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln Phe Pro  
 675 680 685  
 Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe Leu Thr

690	695	700
Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu Leu Ser		
705	710	715 720
His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu Val Ser		
	725	730 735
Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr Ile Asn		
	740	745 750
Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met Leu Glu		
	755	760 765
Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp Phe Arg		
	770	775 780
Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu Val Asp		
	785	790 795 800
Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser		
	805	810 815
Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile Leu Phe		
	820	825 830
Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala		
	835	840 845
His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu		
	850	855 860
Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr		
	865	870 875 880
Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr Asp Trp		
	885	890 895
Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp Lys Asn		
	900	905 910
Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile		
	915	920 925
Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe		
	930	935 940
Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe		
	945	950 955 960
Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile		
	965	970 975
Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu		
	980	985 990
Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro		
	995	1000 1005
Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn Val Val Leu		
	1010	1015 1020
Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met Tyr Val Asp Ser Ile		

1025  
Lys Gln Tyr  
1040

1030

1035

<210> 51  
<211> 1059  
<212> PRT  
<213> Homo sapiens

<400> 51

Met Lys Glu Ser Ser Leu Gln Asn Ser Ser Cys Ser Leu Gly Lys Glu  
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Thr Lys Lys Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile  
20 25 30  
Phe Leu Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe  
35 40 45  
Ser Arg Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile  
50 55 60  
Ala Glu Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly  
65 70 75 80  
Lys Tyr Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile  
85 90 95  
Thr Asn Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu  
100 105 110  
Asn His Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln  
115 120 125  
Ser Asn Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn  
130 135 140  
Leu Arg Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser  
145 150 155 160  
Gly Leu Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile  
165 170 175  
Tyr Asn Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn  
180 185 190  
Leu Tyr Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr  
195 200 205  
Asn Ile Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu  
210 215 220  
Ser Leu Ser Phe Asn Ser Leu Ser His Val Ser Pro Lys Leu Pro Ser  
225 230 235 240  
Ser Leu Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser  
245 250 255  
Glu Glu Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser  
260 265 270



Gly Asn Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys  
 275 280 285  
 Asp Gly Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu  
 290 295 300  
 Thr Gln Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile  
 305 310 315 320  
 Asn Ala Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu  
 325 330 335  
 Glu Phe Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr  
 340 345 350  
 Met Leu Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys  
 355 360 365  
 Gly Ser Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Pro  
 370 375 380  
 Leu Ser Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu  
 385 390 395 400  
 Arg Glu Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr  
 405 410 415  
 Ile Asn Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe  
 420 425 430  
 Gln Asn Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile  
 435 440 445  
 Ser Pro Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser  
 450 455 460  
 Phe Gln Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp  
 465 470 475 480  
 Pro His Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln  
 485 490 495  
 Cys Ala Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe  
 500 505 510  
 Phe Ile Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu  
 515 520 525  
 Asn Leu Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe  
 530 535 540  
 Ser Ala Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu  
 545 550 555 560  
 Asp Phe Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val  
 565 570 575  
 Leu Asp Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr  
 580 585 590  
 His His Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn

595	600	605
Leu Ser His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu		
610	615	620
Ser Lys Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile		
625	630	635
Leu Trp Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu		
	645	650
		655
Lys Asn Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile		
	660	665
		670
Pro Asn Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His		
	675	680
		685
Ile Asn Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln		
690	695	700
Phe Pro Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe		
705	710	715
		720
Leu Thr Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu		
	725	730
		735
Leu Ser His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu		
	740	745
		750
Val Ser Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr		
	755	760
		765
Ile Asn Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met		
770	775	780
Leu Glu Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp		
785	790	795
		800
Phe Arg Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu		
	805	810
		815
Val Asp Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile		
	820	825
		830
Val Ser Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile		
	835	840
		845
Leu Phe Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala		
850	855	860
Leu Ala His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val		
865	870	875
		880
Cys Leu Ala Lys Ile Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr		
	885	890
		895
Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr		
	900	905
		910
Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp		
	915	920
		925
Lys Asn Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu		

930                      935                      940  
 Ala Ile Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr  
 945                      950                      955                      960  
 Val Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr  
                          965                      970                      975  
 Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val  
                          980                      985                      990  
 Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu  
                          995                      1000                      1005  
 Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro  
                          1010                      1015                      1020  
 Asp Asn Pro Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn  
                          1025                      1030                      1035  
 Val Val Leu Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met Tyr Val  
                          1040                      1045                      1050  
 Asp Ser Ile Lys Gln Tyr  
                          1055

<210> 52  
 <211> 1041  
 <212> PRT  
 <213> Homo sapiens

<400> 52

Met Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile Phe Leu  
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 Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe Ser Arg  
                          20                      25                      30  
 Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu  
                          35                      40                      45  
 Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr  
                          50                      55                      60  
 Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn  
 65                      70                      75                      80  
 Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His  
                          85                      90                      95  
 Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn  
                          100                      105                      110  
 Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg  
                          115                      120                      125  
 Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu  
                          130                      135                      140  
 Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile Tyr Asn  
 145                      150                      155                      160

Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr  
 165 170 175  
 Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile  
 180 185 190  
 Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu  
 195 200 205  
 Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu  
 210 215 220  
 Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu  
 225 230 235 240  
 Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn  
 245 250 255  
 Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly  
 260 265 270  
 Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln  
 275 280 285  
 Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala  
 290 295 300  
 Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe  
 305 310 315 320  
 Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu  
 325 330 335  
 Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser  
 340 345 350  
 Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser  
 355 360 365  
 Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu  
 370 375 380  
 Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn  
 385 390 395 400  
 Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn  
 405 410 415  
 Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro  
 420 425 430  
 Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln  
 435 440 445  
 Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His  
 450 455 460  
 Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala  
 465 470 475 480  
 Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile

485 490 495  
 Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu Asn Leu  
 500 505 510  
 Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe Ser Ala  
 515 520 525  
 Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu Asp Phe  
 530 535 540  
 Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val Leu Asp  
 545 550 555 560  
 Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr His His  
 565 570 575  
 Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn Leu Ser  
 580 585 590  
 His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu Ser Lys  
 595 600 605  
 Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp  
 610 615 620  
 Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu Lys Asn  
 625 630 635 640  
 Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn  
 645 650 655  
 Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His Ile Asn  
 660 665 670  
 Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln Phe Pro  
 675 680 685  
 Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe Leu Thr  
 690 695 700  
 Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu Leu Ser  
 705 710 715 720  
 His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu Val Ser  
 725 730 735  
 Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr Ile Asn  
 740 745 750  
 Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met Leu Glu  
 755 760 765  
 Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp Phe Arg  
 770 775 780  
 Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu Val Asp  
 785 790 795 800  
 Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser  
 805 810 815  
 Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile Leu Phe

820 825 830  
 Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala  
 835 840 845  
 His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu  
 850 855 860  
 Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr  
 865 870 875 880  
 Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr Asp Trp  
 885 890 895  
 Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp Lys Asn  
 900 905 910  
 Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile  
 915 920 925  
 Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe  
 930 935 940  
 Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe  
 945 950 955 960  
 Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile  
 965 970 975  
 Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu  
 980 985 990  
 Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro  
 995 1000 1005  
 Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn Val Val Leu  
 1010 1015 1020  
 Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met Tyr Val Asp Ser Ile  
 1025 1030 1035  
 Lys Gln Tyr  
 1040

<210> 53  
 <211> 1041  
 <212> PRT  
 <213> Homo sapiens

<400> 53

Met Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile Phe Leu  
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 Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe Ser Arg  
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 Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu  
 35 40 45  
 Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr  
 50 55 60

Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn  
 65 70 75 80  
 Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His  
 85 90 95  
 Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn  
 100 105 110  
 Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg  
 115 120 125  
 Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu  
 130 135 140  
 Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile Tyr Asn  
 145 150 155 160  
 Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr  
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agaaaacttg ttttggcaaa gtctgaaaaa tgtggtcttg actgaaaatg attcacggta	3120
tgacgatttg tacattgatt ccattaggca atactagtga tgggaagtca cgactctgcc	3180



atcataaaaa cacacagctt ctctttacaa tgaaccgaat

3220

&lt;210&gt; 57

&lt;211&gt; 1032

&lt;212&gt; PRT

&lt;213&gt; murine

&lt;400&gt; 57

Met Glu Asn Met Pro Pro Gln Ser Trp Ile Leu Thr Cys Phe Cys Leu  
1 5 10 15

Leu Ser Ser Gly Thr Ser Ala Ile Phe His Lys Ala Asn Tyr Ser Arg  
20 25 30

Ser Tyr Pro Cys Asp Glu Ile Arg His Asn Ser Leu Val Ile Ala Glu  
35 40 45

Cys Asn His Arg Gln Leu His Glu Val Pro Gln Thr Ile Gly Lys Tyr  
50 55 60

Val Thr Asn Ile Asp Leu Ser Asp Asn Ala Ile Thr His Ile Thr Lys  
65 70 75 80

Glu Ser Phe Gln Lys Leu Gln Asn Leu Thr Lys Ile Asp Leu Asn His  
85 90 95

Asn Ala Lys Gln Gln His Pro Asn Glu Asn Lys Asn Gly Met Asn Ile  
100 105 110

Thr Glu Gly Ala Leu Leu Ser Leu Arg Asn Leu Thr Val Leu Leu Leu  
115 120 125

Glu Asp Asn Gln Leu Tyr Thr Ile Pro Ala Gly Leu Pro Glu Ser Leu  
130 135 140

Lys Glu Leu Ser Leu Ile Gln Asn Asn Ile Phe Gln Val Thr Lys Asn  
145 150 155 160

Asn Thr Phe Gly Leu Arg Asn Leu Glu Arg Leu Tyr Leu Gly Trp Asn  
165 170 175

Cys Tyr Phe Lys Cys Asn Gln Thr Phe Lys Val Glu Asp Gly Ala Phe  
180 185 190

Lys Asn Leu Ile His Leu Lys Val Leu Ser Leu Ser Phe Asn Asn Leu  
195 200 205

Phe Tyr Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu  
210 215 220

Ser Asn Ala Lys Ile Met Asn Ile Thr Gln Glu Asp Phe Lys Gly Leu  
225 230 235 240

Glu Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Tyr  
245 250 255

Asn Ala Pro Phe Pro Cys Thr Pro Cys Lys Glu Asn Ser Ser Ile His  
260 265 270

Ile His Pro Leu Ala Phe Gln Ser Leu Thr Gln Leu Leu Tyr Leu Asn  
 275 280 285  
 Leu Ser Ser Thr Ser Leu Arg Thr Ile Pro Ser Thr Trp Phe Glu Asn  
 290 295 300  
 Leu Ser Asn Leu Lys Glu Leu His Leu Glu Phe Asn Tyr Leu Val Gln  
 305 310 315 320  
 Glu Ile Ala Ser Gly Ala Phe Leu Thr Lys Leu Pro Ser Leu Gln Ile  
 325 330 335  
 Leu Asp Leu Ser Phe Asn Phe Gln Tyr Lys Glu Tyr Leu Gln Phe Ile  
 340 345 350  
 Asn Ile Ser Ser Asn Phe Ser Lys Leu Arg Ser Leu Lys Lys Leu His  
 355 360 365  
 Leu Arg Gly Tyr Val Phe Arg Glu Leu Lys Lys Lys His Phe Glu His  
 370 375 380  
 Leu Gln Ser Leu Pro Asn Leu Ala Thr Ile Asn Leu Gly Ile Asn Phe  
 385 390 395 400  
 Ile Glu Lys Ile Asp Phe Lys Ala Phe Gln Asn Phe Ser Lys Leu Asp  
 405 410 415  
 Val Ile Tyr Leu Ser Gly Asn Arg Ile Ala Ser Val Leu Asp Gly Thr  
 420 425 430  
 Asp Tyr Ser Ser Trp Arg Asn Arg Leu Arg Lys Pro Leu Ser Thr Asp  
 435 440 445  
 Asp Asp Glu Phe Asp Pro His Val Asn Phe Tyr His Ser Thr Lys Pro  
 450 455 460  
 Leu Ile Lys Pro Gln Cys Thr Ala Tyr Gly Lys Ala Leu Asp Leu Ser  
 465 470 475 480  
 Leu Asn Asn Ile Phe Ile Ile Gly Lys Ser Gln Phe Glu Gly Phe Gln  
 485 490 495  
 Asp Ile Ala Cys Leu Asn Leu Ser Phe Asn Ala Asn Thr Gln Val Phe  
 500 505 510  
 Asn Gly Thr Glu Phe Ser Ser Met Pro His Ile Lys Tyr Leu Asp Leu  
 515 520 525  
 Thr Asn Asn Arg Leu Asp Phe Asp Asp Asn Asn Ala Phe Ser Asp Leu  
 530 535 540  
 His Asp Leu Glu Val Leu Asp Leu Ser His Asn Ala His Tyr Phe Ser  
 545 550 555 560  
 Ile Ala Gly Val Thr His Arg Leu Gly Phe Ile Gln Asn Leu Ile Asn  
 565 570 575  
 Leu Arg Val Leu Asn Leu Ser His Asn Gly Ile Tyr Thr Leu Thr Glu  
 580 585 590  
 Glu Ser Glu Leu Lys Ser Ile Ser Leu Lys Glu Leu Val Phe Ser Gly

595 600 605  
 Asn Arg Leu Asp His Leu Trp Asn Ala Asn Asp Gly Lys Tyr Trp Ser  
 610 615 620  
 Ile Phe Lys Ser Leu Gln Asn Leu Ile Arg Leu Asp Leu Ser Tyr Asn  
 625 630 635 640  
 Asn Leu Gln Gln Ile Pro Asn Gly Ala Phe Leu Asn Leu Pro Gln Ser  
 645 650 655  
 Leu Gln Glu Leu Leu Ile Ser Gly Asn Lys Leu Arg Phe Phe Asn Trp  
 660 665 670  
 Thr Leu Leu Gln Tyr Phe Pro His Leu His Leu Leu Asp Leu Ser Arg  
 675 680 685  
 Asn Glu Leu Tyr Phe Leu Pro Asn Cys Leu Ser Lys Phe Ala His Ser  
 690 695 700  
 Leu Glu Thr Leu Leu Leu Ser His Asn His Phe Ser His Leu Pro Ser  
 705 710 715 720  
 Gly Phe Leu Ser Glu Ala Arg Asn Leu Val His Leu Asp Leu Ser Phe  
 725 730 735  
 Asn Thr Ile Lys Met Ile Asn Lys Ser Ser Leu Gln Thr Lys Met Lys  
 740 745 750  
 Thr Asn Leu Ser Ile Leu Glu Leu His Gly Asn Tyr Phe Asp Cys Thr  
 755 760 765  
 Cys Asp Ile Ser Asp Phe Arg Ser Trp Leu Asp Glu Asn Leu Asn Ile  
 770 775 780  
 Thr Ile Pro Lys Leu Val Asn Val Ile Cys Ser Asn Pro Gly Asp Gln  
 785 790 795 800  
 Lys Ser Lys Ser Ile Met Ser Leu Asp Leu Thr Thr Cys Val Ser Asp  
 805 810 815  
 Thr Thr Ala Ala Val Leu Phe Phe Leu Thr Phe Leu Thr Thr Ser Met  
 820 825 830  
 Val Met Leu Ala Ala Leu Val His His Leu Phe Tyr Trp Asp Val Trp  
 835 840 845  
 Phe Ile Tyr His Met Cys Ser Ala Lys Leu Lys Gly Tyr Arg Thr Ser  
 850 855 860  
 Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys  
 865 870 875 880  
 Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu  
 885 890 895  
 Glu Glu Ser Glu Asp Lys Ser Val Leu Leu Cys Leu Glu Glu Arg Asp  
 900 905 910  
 Trp Asp Pro Gly Leu Pro Ile Ile Asp Asn Leu Met Gln Ser Ile Asn  
 915 920 925  
 Gln Ser Lys Lys Thr Ile Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser

930                      935                      940  
 Trp Asn Phe Lys Thr Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp  
 945                      950                      955                      960  
  
 Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln  
                          965                      970                      975  
  
 Tyr Ser Gln Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile  
                          980                      985                      990  
  
 Leu Gln Trp Pro Asn Asn Pro Lys Ala Glu Asn Leu Phe Trp Gln Ser  
                          995                      1000                      1005  
  
 Leu Lys Asn Val Val Leu Thr Glu Asn Asp Ser Arg Tyr Asp Asp  
                          1010                      1015                      1020  
  
 Leu Tyr Ile Asp Ser Ile Arg Gln Tyr  
                          1025                      1030

<210> 58  
 <211> 1032  
 <212> PRT  
 <213> murine

<400> 58

Met Glu Asn Met Pro Pro Gln Ser Trp Ile Leu Thr Cys Phe Cys Leu  
 1                      5                      10                      15  
  
 Leu Ser Ser Gly Thr Ser Ala Ile Phe His Lys Ala Asn Tyr Ser Arg  
                          20                      25                      30  
  
 Ser Tyr Pro Cys Asp Glu Ile Arg His Asn Ser Leu Val Ile Ala Glu  
                          35                      40                      45  
  
 Cys Asn His Arg Gln Leu His Glu Val Pro Gln Thr Ile Gly Lys Tyr  
                          50                      55                      60  
  
 Val Thr Asn Ile Asp Leu Ser Asp Asn Ala Ile Thr His Ile Thr Lys  
 65                      70                      75                      80  
  
 Glu Ser Phe Gln Lys Leu Gln Asn Leu Thr Lys Ile Asp Leu Asn His  
                          85                      90                      95  
  
 Asn Ala Lys Gln Gln His Pro Asn Glu Asn Lys Asn Gly Met Asn Ile  
                          100                      105                      110  
  
 Thr Glu Gly Ala Leu Leu Ser Leu Arg Asn Leu Thr Val Leu Leu Leu  
                          115                      120                      125  
  
 Glu Asp Asn Gln Leu Tyr Thr Ile Pro Ala Gly Leu Pro Glu Ser Leu  
                          130                      135                      140  
  
 Lys Glu Leu Ser Leu Ile Gln Asn Asn Ile Phe Gln Val Thr Lys Asn  
 145                      150                      155                      160  
  
 Asn Thr Phe Gly Leu Arg Asn Leu Glu Arg Leu Tyr Leu Gly Trp Asn  
                          165                      170                      175  
  
 Cys Tyr Phe Lys Cys Asn Gln Thr Phe Lys Val Glu Asp Gly Ala Phe  
                          180                      185                      190

Lys Asn Leu Ile His Leu Lys Val Leu Ser Leu Ser Phe Asn Asn Leu  
 195 200 205  
 Phe Tyr Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu  
 210 215 220  
 Ser Asn Ala Lys Ile Met Asn Ile Thr Gln Glu Asp Phe Lys Gly Leu  
 225 230 235 240  
 Glu Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Tyr  
 245 250 255  
 Asn Ala Pro Phe Pro Cys Thr Pro Cys Lys Glu Asn Ser Ser Ile His  
 260 265 270  
 Ile His Pro Leu Ala Phe Gln Ser Leu Thr Gln Leu Leu Tyr Leu Asn  
 275 280 285  
 Leu Ser Ser Thr Ser Leu Arg Thr Ile Pro Ser Thr Trp Phe Glu Asn  
 290 295 300  
 Leu Ser Asn Leu Lys Glu Leu His Leu Glu Phe Asn Tyr Leu Val Gln  
 305 310 315 320  
 Glu Ile Ala Ser Gly Ala Phe Leu Thr Lys Leu Pro Ser Leu Gln Ile  
 325 330 335  
 Leu Asp Leu Ser Phe Asn Phe Gln Tyr Lys Glu Tyr Leu Gln Phe Ile  
 340 345 350  
 Asn Ile Ser Ser Asn Phe Ser Lys Leu Arg Ser Leu Lys Lys Leu His  
 355 360 365  
 Leu Arg Gly Tyr Val Phe Arg Glu Leu Lys Lys Lys His Phe Glu His  
 370 375 380  
 Leu Gln Ser Leu Pro Asn Leu Ala Thr Ile Asn Leu Gly Ile Asn Phe  
 385 390 395 400  
 Ile Glu Lys Ile Asp Phe Lys Ala Phe Gln Asn Phe Ser Lys Leu Asp  
 405 410 415  
 Val Ile Tyr Leu Ser Gly Asn Arg Ile Ala Ser Val Leu Asp Gly Thr  
 420 425 430  
 Asp Tyr Ser Ser Trp Arg Asn Arg Leu Arg Lys Pro Leu Ser Thr Asp  
 435 440 445  
 Asp Asp Glu Phe Asp Pro His Val Asn Phe Tyr His Ser Thr Lys Pro  
 450 455 460  
 Leu Ile Lys Pro Gln Cys Thr Ala Tyr Gly Lys Ala Leu Asp Leu Ser  
 465 470 475 480  
 Leu Asn Asn Ile Phe Ile Ile Gly Lys Ser Gln Phe Glu Gly Phe Gln  
 485 490 495  
 Asp Ile Ala Cys Leu Asn Leu Ser Phe Asn Ala Asn Thr Gln Val Phe  
 500 505 510  
 Asn Gly Thr Glu Phe Ser Ser Met Pro His Ile Lys Tyr Leu Asp Leu

		515				520						525				
Thr	Asn	Asn	Arg	Leu	Asp	Phe	Asp	Asn	Asn	Ala	Phe	Ser	Asp	Leu		
	530					535				540						
His	Asp	Leu	Glu	Val	Leu	Asp	Leu	Ser	His	Asn	Ala	His	Tyr	Phe	Ser	
545					550					555						560
Ile	Ala	Gly	Val	Thr	His	Arg	Leu	Gly	Phe	Ile	Gln	Asn	Leu	Ile	Asn	
				565					570					575		
Leu	Arg	Val	Leu	Asn	Leu	Ser	His	Asn	Gly	Ile	Tyr	Thr	Leu	Thr	Glu	
			580					585					590			
Glu	Ser	Glu	Leu	Lys	Ser	Ile	Ser	Leu	Lys	Glu	Leu	Val	Phe	Ser	Gly	
		595					600					605				
Asn	Arg	Leu	Asp	His	Leu	Trp	Asn	Ala	Asn	Asp	Gly	Lys	Tyr	Trp	Ser	
	610					615					620					
Ile	Phe	Lys	Ser	Leu	Gln	Asn	Leu	Ile	Arg	Leu	Asp	Leu	Ser	Tyr	Asn	
625					630					635					640	
Asn	Leu	Gln	Gln	Ile	Pro	Asn	Gly	Ala	Phe	Leu	Asn	Leu	Pro	Gln	Ser	
				645					650					655		
Leu	Gln	Glu	Leu	Leu	Ile	Ser	Gly	Asn	Lys	Leu	Arg	Phe	Phe	Asn	Trp	
			660					665					670			
Thr	Leu	Leu	Gln	Tyr	Phe	Pro	His	Leu	His	Leu	Leu	Asp	Leu	Ser	Arg	
		675					680					685				
Asn	Glu	Leu	Tyr	Phe	Leu	Pro	Asn	Cys	Leu	Ser	Lys	Phe	Ala	His	Ser	
	690					695					700					
Leu	Glu	Thr	Leu	Leu	Leu	Ser	His	Asn	His	Phe	Ser	His	Leu	Pro	Ser	
705					710					715					720	
Gly	Phe	Leu	Ser	Glu	Ala	Arg	Asn	Leu	Val	His	Leu	Asp	Leu	Ser	Phe	
				725					730					735		
Asn	Thr	Ile	Lys	Met	Ile	Asn	Lys	Ser	Ser	Leu	Gln	Thr	Lys	Met	Lys	
			740					745					750			
Thr	Asn	Leu	Ser	Ile	Leu	Glu	Leu	His	Gly	Asn	Tyr	Phe	Asp	Cys	Thr	
		755					760					765				
Cys	Asp	Ile	Ser	Asp	Phe	Arg	Ser	Trp	Leu	Asp	Glu	Asn	Leu	Asn	Ile	
	770					775					780					
Thr	Ile	Pro	Lys	Leu	Val	Asn	Val	Ile	Cys	Ser	Asn	Pro	Gly	Asp	Gln	
785					790					795					800	
Lys	Ser	Lys	Ser	Ile	Met	Ser	Leu	Asp	Leu	Thr	Thr	Cys	Val	Ser	Asp	
				805					810					815		
Thr	Thr	Ala	Ala	Val	Leu	Phe	Phe	Leu	Thr	Phe	Leu	Thr	Thr	Ser	Met	
			820					825					830			
Val	Met	Leu	Ala	Ala	Leu	Val	His	His	Leu	Phe	Tyr	Trp	Asp	Val	Trp	
		835					840					845				
Phe	Ile	Tyr	His	Met	Cys	Ser	Ala	Lys	Leu	Lys	Gly	Tyr	Arg	Thr	Ser	

850                      855                      860  
 Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys  
 865                      870                      875                      880  
 Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu  
                          885                      890                      895  
 Glu Glu Ser Glu Asp Lys Ser Val Leu Leu Cys Leu Glu Glu Arg Asp  
                          900                      905                      910  
 Trp Asp Pro Gly Leu Pro Ile Ile Asp Asn Leu Met Gln Ser Ile Asn  
                          915                      920                      925  
 Gln Ser Lys Lys Thr Ile Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser  
                          930                      935                      940  
 Trp Asn Phe Lys Thr Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp  
 945                      950                      955                      960  
 Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln  
                          965                      970                      975  
 Tyr Ser Gln Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile  
                          980                      985                      990  
 Leu Gln Trp Pro Asn Asn Pro Lys Ala Glu Asn Leu Phe Trp Gln Ser  
                          995                      1000                      1005  
 Leu Lys Asn Val Val Leu Thr Glu Asn Asp Ser Arg Tyr Asp Asp  
                          1010                      1015                      1020  
 Leu Tyr Ile Asp Ser Ile Arg Gln Tyr  
                          1025                      1030

<210> 59  
 <211> 1032  
 <212> PRT  
 <213> murine

<400> 59

Met Glu Asn Met Pro Pro Gln Ser Trp Ile Leu Thr Cys Phe Cys Leu  
 1                      5                      10                      15  
 Leu Ser Ser Gly Thr Ser Ala Ile Phe His Lys Ala Asn Tyr Ser Arg  
                          20                      25                      30  
 Ser Tyr Pro Cys Asp Glu Ile Arg His Asn Ser Leu Val Ile Ala Glu  
                          35                      40                      45  
 Cys Asn His Arg Gln Leu His Glu Val Pro Gln Thr Ile Gly Lys Tyr  
                          50                      55                      60  
 Val Thr Asn Ile Asp Leu Ser Asp Asn Ala Ile Thr His Ile Thr Lys  
 65                      70                      75                      80  
 Glu Ser Phe Gln Lys Leu Gln Asn Leu Thr Lys Ile Asp Leu Asn His  
                          85                      90                      95  
 Asn Ala Lys Gln Gln His Pro Asn Glu Asn Lys Asn Gly Met Asn Ile  
                          100                      105                      110

Thr Glu Gly Ala Leu Leu Ser Leu Arg Asn Leu Thr Val Leu Leu Leu  
 115 120 125  
 Glu Asp Asn Gln Leu Tyr Thr Ile Pro Ala Gly Leu Pro Glu Ser Leu  
 130 135 140  
 Lys Glu Leu Ser Leu Ile Gln Asn Asn Ile Phe Gln Val Thr Lys Asn  
 145 150 155 160  
 Asn Thr Phe Gly Leu Arg Asn Leu Glu Arg Leu Tyr Leu Gly Trp Asn  
 165 170 175  
 Cys Tyr Phe Lys Cys Asn Gln Thr Phe Lys Val Glu Asp Gly Ala Phe  
 180 185 190  
 Lys Asn Leu Ile His Leu Lys Val Leu Ser Leu Ser Phe Asn Asn Leu  
 195 200 205  
 Phe Tyr Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu  
 210 215 220  
 Ser Asn Ala Lys Ile Met Asn Ile Thr Gln Glu Asp Phe Lys Gly Leu  
 225 230 235 240  
 Glu Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Tyr  
 245 250 255  
 Asn Ala Pro Phe Pro Cys Thr Pro Cys Lys Glu Asn Ser Ser Ile His  
 260 265 270  
 Ile His Pro Leu Ala Phe Gln Ser Leu Thr Gln Leu Leu Tyr Leu Asn  
 275 280 285  
 Leu Ser Ser Thr Ser Leu Arg Thr Ile Pro Ser Thr Trp Phe Glu Asn  
 290 295 300  
 Leu Ser Asn Leu Lys Glu Leu His Leu Glu Phe Asn Tyr Leu Val Gln  
 305 310 315 320  
 Glu Ile Ala Ser Gly Ala Phe Leu Thr Lys Leu Pro Ser Leu Gln Ile  
 325 330 335  
 Leu Asp Leu Ser Phe Asn Phe Gln Tyr Lys Glu Tyr Leu Gln Phe Ile  
 340 345 350  
 Asn Ile Ser Ser Asn Phe Ser Lys Leu Arg Ser Leu Lys Lys Leu His  
 355 360 365  
 Leu Arg Gly Tyr Val Phe Arg Glu Leu Lys Lys Lys His Phe Glu His  
 370 375 380  
 Leu Gln Ser Leu Pro Asn Leu Ala Thr Ile Asn Leu Gly Ile Asn Phe  
 385 390 395 400  
 Ile Glu Lys Ile Asp Phe Lys Ala Phe Gln Asn Phe Ser Lys Leu Asp  
 405 410 415  
 Val Ile Tyr Leu Ser Gly Asn Arg Ile Ala Ser Val Leu Asp Gly Thr  
 420 425 430  
 Asp Tyr Ser Ser Trp Arg Asn Arg Leu Arg Lys Pro Leu Ser Thr Asp



435 440 445  
 Asp Asp Glu Phe Asp Pro His Val Asn Phe Tyr His Ser Thr Lys Pro  
 450 455 460  
 Leu Ile Lys Pro Gln Cys Thr Ala Tyr Gly Lys Ala Leu Asp Leu Ser  
 465 470 475 480  
 Leu Asn Asn Ile Phe Ile Ile Gly Lys Ser Gln Phe Glu Gly Phe Gln  
 485 490 495  
 Asp Ile Ala Cys Leu Asn Leu Ser Phe Asn Ala Asn Thr Gln Val Phe  
 500 505 510  
 Asn Gly Thr Glu Phe Ser Ser Met Pro His Ile Lys Tyr Leu Asp Leu  
 515 520 525  
 Thr Asn Asn Arg Leu Asp Phe Asp Asp Asn Asn Ala Phe Ser Asp Leu  
 530 535 540  
 His Asp Leu Glu Val Leu Asp Leu Ser His Asn Ala His Tyr Phe Ser  
 545 550 555 560  
 Ile Ala Gly Val Thr His Arg Leu Gly Phe Ile Gln Asn Leu Ile Asn  
 565 570 575  
 Leu Arg Val Leu Asn Leu Ser His Asn Gly Ile Tyr Thr Leu Thr Glu  
 580 585 590  
 Glu Ser Glu Leu Lys Ser Ile Ser Leu Lys Glu Leu Val Phe Ser Gly  
 595 600 605  
 Asn Arg Leu Asp His Leu Trp Asn Ala Asn Asp Gly Lys Tyr Trp Ser  
 610 615 620  
 Ile Phe Lys Ser Leu Gln Asn Leu Ile Arg Leu Asp Leu Ser Tyr Asn  
 625 630 635 640  
 Asn Leu Gln Gln Ile Pro Asn Gly Ala Phe Leu Asn Leu Pro Gln Ser  
 645 650 655  
 Leu Gln Glu Leu Leu Ile Ser Gly Asn Lys Leu Arg Phe Phe Asn Trp  
 660 665 670  
 Thr Leu Leu Gln Tyr Phe Pro His Leu His Leu Leu Asp Leu Ser Arg  
 675 680 685  
 Asn Glu Leu Tyr Phe Leu Pro Asn Cys Leu Ser Lys Phe Ala His Ser  
 690 695 700  
 Leu Glu Thr Leu Leu Leu Ser His Asn His Phe Ser His Leu Pro Ser  
 705 710 715 720  
 Gly Phe Leu Ser Glu Ala Arg Asn Leu Val His Leu Asp Leu Ser Phe  
 725 730 735  
 Asn Thr Ile Lys Met Ile Asn Lys Ser Ser Leu Gln Thr Lys Met Lys  
 740 745 750  
 Thr Asn Leu Ser Ile Leu Glu Leu His Gly Asn Tyr Phe Asp Cys Thr  
 755 760 765  
 Cys Asp Ile Ser Asp Phe Arg Ser Trp Leu Asp Glu Asn Leu Asn Ile

770                      775                      780  
 Thr Ile Pro Lys Leu Val Asn Val Ile Cys Ser Asn Pro Gly Asp Gln  
 785                      790                      795                      800  
  
 Lys Ser Lys Ser Ile Met Ser Leu Asp Leu Thr Thr Cys Val Ser Asp  
                     805                      810                      815  
  
 Thr Thr Ala Ala Val Leu Phe Phe Leu Thr Phe Leu Thr Thr Ser Met  
                     820                      825                      830  
  
 Val Met Leu Ala Ala Leu Val His His Leu Phe Tyr Trp Asp Val Trp  
                     835                      840                      845  
  
 Phe Ile Tyr His Met Cys Ser Ala Lys Leu Lys Gly Tyr Arg Thr Ser  
                     850                      855                      860  
  
 Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys  
 865                      870                      875                      880  
  
 Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu  
                     885                      890                      895  
  
 Glu Glu Ser Glu Asp Lys Ser Val Leu Leu Cys Leu Glu Glu Arg Asp  
                     900                      905                      910  
  
 Trp Asp Pro Gly Leu Pro Ile Ile Asp Asn Leu Met Gln Ser Ile Asn  
                     915                      920                      925  
  
 Gln Ser Lys Lys Thr Ile Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser  
                     930                      935                      940  
  
 Trp Asn Phe Lys Thr Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp  
 945                      950                      955                      960  
  
 Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln  
                     965                      970                      975  
  
 Tyr Ser Gln Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile  
                     980                      985                      990  
  
 Leu Gln Trp Pro Asn Asn Pro Lys Ala Glu Asn Leu Phe Trp Gln Ser  
                     995                      1000                      1005  
  
 Leu Lys Asn Val Val Leu Thr Glu Asn Asp Ser Arg Tyr Asp Asp  
                     1010                      1015                      1020  
  
 Leu Tyr Ile Asp Ser Ile Arg Gln Tyr  
                     1025                      1030

&lt;210&gt; 60

&lt;211&gt; 3352

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 60

aggctggtat aaaaatctta cttcctctat tctctgagcc gctgctgccc ctgtgggaag 60

ggacctcgag tgtgaagcat ccttcctgt agctgctgtc cagtctgccc gccagaccct 120

ctggagaagc cctgcccc cagcatgggt ttctgccgca gcgccctgca cccgctgtct 180

ctcctgggtgc	aggccatcat	gctggccatg	accctggccc	tgggtacctt	gcctgccttc	240
ctaccctgtg	agctccagcc	ccacggcctg	gtgaactgca	actggctgtt	cctgaagtct	300
gtgccccact	tctccatggc	agcaccctcg	ggcaatgtca	ccagcctttc	cttgtcctcc	360
aaccgcatcc	accacctcca	tgattctgac	tttgcccacc	tgcccagcct	gcggcatctc	420
aacctcaagt	ggaactgccc	gccggttggc	ctcagcccca	tgcacttccc	ctgccacatg	480
accatcgagc	ccagcacctt	cttggctgtg	cccaccctgg	aagagctaaa	cctgagctac	540
aacaacatca	tgactgtgcc	tgcgctgccc	aaatccctca	tatccctgtc	cctcagccat	600
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<211> 3257

<212> DNA

<213> Homo sapiens

<400> 61

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<210> 62  
 <211> 1032  
 <212> PRT  
 <213> Homo sapiens

<400> 62

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 Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu  
 35 40 45  
 Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn  
 50 55 60  
 Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp  
 65 70 75 80  
 Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp  
 85 90 95  
 Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met

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Asn	Leu	Ser	Tyr	Asn	Asn	Ile	Met	Thr	Val	Pro	Ala	Leu	Pro	Lys	Ser
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Leu	Ile	Ser	Leu	Ser	Leu	Ser	His	Thr	Asn	Ile	Leu	Met	Leu	Asp	Ser
145					150					155					160
Ala	Ser	Leu	Ala	Gly	Leu	His	Ala	Leu	Arg	Phe	Leu	Phe	Met	Asp	Gly
				165					170					175	
Asn	Cys	Tyr	Tyr	Lys	Asn	Pro	Cys	Arg	Gln	Ala	Leu	Glu	Val	Ala	Pro
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Gly	Ala	Leu	Leu	Gly	Leu	Gly	Asn	Leu	Thr	His	Leu	Ser	Leu	Lys	Tyr
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Asn	Asn	Leu	Thr	Val	Val	Pro	Arg	Asn	Leu	Pro	Ser	Ser	Leu	Glu	Tyr
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Leu	Leu	Leu	Ser	Tyr	Asn	Arg	Ile	Val	Lys	Leu	Ala	Pro	Glu	Asp	Leu
225					230					235					240
Ala	Asn	Leu	Thr	Ala	Leu	Arg	Val	Leu	Asp	Val	Gly	Gly	Asn	Cys	Arg
				245					250					255	
Arg	Cys	Asp	His	Ala	Pro	Asn	Pro	Cys	Met	Glu	Cys	Pro	Arg	His	Phe
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Pro	Gln	Leu	His	Pro	Asp	Thr	Phe	Ser	His	Leu	Ser	Arg	Leu	Glu	Gly
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Arg	Gly	Leu	Gly	Asn	Leu	Arg	Val	Leu	Asp	Leu	Ser	Glu	Asn	Phe	Leu
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Tyr	Lys	Cys	Ile	Thr	Lys	Thr	Lys	Ala	Phe	Gln	Gly	Leu	Thr	Gln	Leu
			325						330					335	
Arg	Lys	Leu	Asn	Leu	Ser	Phe	Asn	Tyr	Gln	Lys	Arg	Val	Ser	Phe	Ala
			340					345					350		
His	Leu	Ser	Leu	Ala	Pro	Ser	Phe	Gly	Ser	Leu	Val	Ala	Leu	Lys	Glu
	355						360					365			
Leu	Asp	Met	His	Gly	Ile	Phe	Phe	Arg	Ser	Leu	Asp	Glu	Thr	Thr	Leu
	370				375						380				
Arg	Pro	Leu	Ala	Arg	Leu	Pro	Met	Leu	Gln	Thr	Leu	Arg	Leu	Gln	Met
385					390					395					400
Asn	Phe	Ile	Asn	Gln	Ala	Gln	Leu	Gly	Ile	Phe	Arg	Ala	Phe	Pro	Gly
			405						410					415	
Leu	Arg	Tyr	Val	Asp	Leu	Ser	Asp	Asn	Arg	Ile	Ser	Gly	Ala	Ser	Glu
			420					425					430		
Leu	Thr	Ala	Thr	Met	Gly	Glu	Ala	Asp	Gly	Gly	Glu	Lys	Val	Trp	Leu

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 450 455 460  
 Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser  
 465 470 475 480  
 Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser  
 485 490 495  
 His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val  
 500 505 510  
 Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu  
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 Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu  
 530 535 540  
 Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly  
 545 550 555 560  
 Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr  
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 Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser  
 580 585 590  
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 595 600 605  
 Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe  
 610 615 620  
 Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu  
 625 630 635 640  
 His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln  
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 Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser  
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 Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg  
 675 680 685  
 Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg  
 690 695 700  
 Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe  
 705 710 715 720  
 Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala  
 725 730 735  
 Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu  
 740 745 750  
 Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala  
 755 760 765  
 Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu



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Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser
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      805              810              815

Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val
      820              825              830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
      835              840              845

Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp
      850              855              860

Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln
865              870              875              880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu
      885              890              895

Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp
      900              905              910

Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr
      915              920              925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
      930              935              940

Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945              950              955              960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg
      965              970              975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
      980              985              990

Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln
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Leu Gly Met Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg
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Asn Phe Cys Gln Gly Pro Thr Ala Glu
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<210> 63
<211> 1032
<212> PRT
<213> Homo sapiens

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<400> 63

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      20              25              30

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 50 55 60  
 Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp  
 65 70 75 80  
 Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp  
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 Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met  
 100 105 110  
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 115 120 125  
 Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser  
 130 135 140  
 Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser  
 145 150 155 160  
 Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly  
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 Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro  
 180 185 190  
 Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr  
 195 200 205  
 Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr  
 210 215 220  
 Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu  
 225 230 235 240  
 Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg  
 245 250 255  
 Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe  
 260 265 270  
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 275 280 285  
 Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe  
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 Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu  
 305 310 315 320  
 Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu  
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 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala  
 340 345 350  
 His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu

355 360 365  
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 405 410 415  
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 420 425 430  
 Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu  
 435 440 445  
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 450 455 460  
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 465 470 475 480  
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 485 490 495  
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 500 505 510  
 Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu  
 515 520 525  
 Ser His Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu  
 530 535 540  
 Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly  
 545 550 555 560  
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 565 570 575  
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 Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn  
 595 600 605  
 Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe  
 610 615 620  
 Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu  
 625 630 635 640  
 His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln  
 645 650 655  
 Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser  
 660 665 670  
 Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Gln  
 675 680 685  
 Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg

690 695 700  
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 705 710 715 720  
 Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala  
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 740 745 750  
 Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala  
 755 760 765  
 Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu  
 770 775 780  
 Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser  
 785 790 795 800  
 Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp  
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 Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val  
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 Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His  
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 Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp  
 850 855 860  
 Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln  
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 Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu  
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 Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp  
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 Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser  
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 Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu  
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 Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg  
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 Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val  
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 Asn Phe Cys Gln Gly Pro Thr Ala Glu

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 <213> Homo sapiens  
  
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                     20                      25                      30  
  
 Pro Leu Ser Leu Leu Val Gln Ala Ile Met Leu Ala Met Thr Leu Ala  
                     35                      40                      45  
  
 Leu Gly Thr Leu Pro Ala Phe Leu Pro Cys Glu Leu Gln Pro His Gly  
                     50                      55                      60  
  
 Leu Val Asn Cys Asn Trp Leu Phe Leu Lys Ser Val Pro His Phe Ser  
 65                      70                      75                      80  
  
 Met Ala Ala Pro Arg Gly Asn Val Thr Ser Leu Ser Leu Ser Ser Asn  
                     85                      90                      95  
  
 Arg Ile His His Leu His Asp Ser Asp Phe Ala His Leu Pro Ser Leu  
                     100                      105                      110  
  
 Arg His Leu Asn Leu Lys Trp Asn Cys Pro Pro Val Gly Leu Ser Pro  
                     115                      120                      125  
  
 Met His Phe Pro Cys His Met Thr Ile Glu Pro Ser Thr Phe Leu Ala  
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 Val Pro Thr Leu Glu Glu Leu Asn Leu Ser Tyr Asn Asn Ile Met Thr  
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 Val Pro Ala Leu Pro Lys Ser Leu Ile Ser Leu Ser Leu Ser His Thr  
                     165                      170                      175  
  
 Asn Ile Leu Met Leu Asp Ser Ala Ser Leu Ala Gly Leu His Ala Leu  
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 Arg Phe Leu Phe Met Asp Gly Asn Cys Tyr Tyr Lys Asn Pro Cys Arg  
                     195                      200                      205  
  
 Gln Ala Leu Glu Val Ala Pro Gly Ala Leu Leu Gly Leu Gly Asn Leu  
                     210                      215                      220  
  
 Thr His Leu Ser Leu Lys Tyr Asn Asn Leu Thr Val Val Pro Arg Asn  
 225                      230                      235                      240  
  
 Leu Pro Ser Ser Leu Glu Tyr Leu Leu Leu Ser Tyr Asn Arg Ile Val  
                     245                      250                      255  
  
 Lys Leu Ala Pro Glu Asp Leu Ala Asn Leu Thr Ala Leu Arg Val Leu  
                     260                      265                      270  
  
 Asp Val Gly Gly Asn Cys Arg Arg Cys Asp His Ala Pro Asn Pro Cys  
                     275                      280                      285

Met Glu Cys Pro Arg His Phe Pro Gln Leu His Pro Asp Thr Phe Ser  
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His Leu Ser Arg Leu Glu Gly Leu Val Leu Lys Asp Ser Ser Leu Ser  
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Trp Leu Asn Ala Ser Trp Phe Arg Gly Leu Gly Asn Leu  
 325 330

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 <211> 216  
 <212> PRT  
 <213> Homo sapiens

<400> 65

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Asp Phe His Leu Glu Ile Ala Lys Lys Gly Phe Cys Arg Ser Ala Leu  
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His Pro Leu Ser Leu Leu Val Gln Ala Ile Met Leu Ala Met Thr Leu  
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Ala Leu Gly Thr Leu Pro Ala Phe Leu Pro Cys Glu Leu Gln Pro His  
 50 55 60

Gly Leu Val Asn Cys Asn Trp Leu Phe Leu Lys Ser Val Pro His Phe  
 65 70 75 80

Ser Met Ala Ala Pro Arg Gly Asn Val Thr Ser Leu Ser Leu Ser Ser  
 85 90 95

Asn Arg Ile His His Leu His Asp Ser Asp Phe Ala His Leu Pro Ser  
 100 105 110

Leu Arg His Leu Asn Leu Lys Trp Asn Cys Pro Pro Val Gly Leu Ser  
 115 120 125

Pro Met His Phe Pro Cys His Met Thr Ile Glu Pro Ser Thr Phe Leu  
 130 135 140

Ala Val Pro Thr Leu Glu Glu Leu Asn Leu Ser Tyr Asn Asn Ile Met  
 145 150 155 160

Thr Val Pro Ala Leu Pro Lys Ser Leu Ile Ser Leu Ser Leu Ser His  
 165 170 175

Thr Asn Ile Leu Met Leu Asp Ser Ala Ser Leu Ala Gly Leu His Ala  
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Arg Gln Ala Leu Glu Val Ala Pro  
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<210> 66

<211> 117  
 <212> PRT  
 <213> Homo sapiens

<400> 66

Met Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala  
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Phe Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp  
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Leu Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly  
 35 40 45

Asn Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His  
 50 55 60

Asp Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys  
 65 70 75 80

Trp Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His  
 85 90 95

Met Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu  
 100 105 110

Leu Asn Leu Ser Tyr  
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<210> 67  
 <211> 1032  
 <212> PRT  
 <213> Homo sapiens

<400> 67

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Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe  
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Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu  
 35 40 45

Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn  
 50 55 60

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp  
 65 70 75 80

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp  
 85 90 95

Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met  
 100 105 110

Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu  
 115 120 125

Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser  
 130 135 140  
 Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser  
 145 150 155 160  
 Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly  
 165 170 175  
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 180 185 190  
 Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr  
 195 200 205  
 Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr  
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 Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly  
 275 280 285  
 Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe  
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 Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu  
 305 310 315 320  
 Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu  
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 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala  
 340 345 350  
 His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu  
 355 360 365  
 Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu  
 370 375 380  
 Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met  
 385 390 395 400  
 Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly  
 405 410 415  
 Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu  
 420 425 430  
 Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu  
 435 440 445  
 Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu



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 Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser  
 465                      470                      475                      480  
  
 Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser  
                     485                      490                      495  
  
 His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val  
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 Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu  
                     515                      520                      525  
  
 Ser His Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu  
                     530                      535                      540  
  
 Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly  
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 Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr  
                     565                      570                      575  
  
 Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser  
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 Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn  
                     595                      600                      605  
  
 Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe  
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 Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu  
 625                      630                      635                      640  
  
 His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln  
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 Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser  
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 Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Gln  
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 Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg  
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 Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe  
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 Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala  
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 Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu  
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 Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala  
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 Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu  
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785                      790                      795                      800  
 Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp  
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 Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val  
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 Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His  
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 Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp  
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 Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln  
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 Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr  
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 Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu  
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 <212> DNA  
 <213> murine

<400> 68  
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&lt;210&gt; 69

&lt;211&gt; 3471

&lt;212&gt; DNA

&lt;213&gt; murine

&lt;400&gt; 69

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Ala Gln Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln
865              870              875              880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu
              885              890              895

Gly Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp
              900              905              910

Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr
              915              920              925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
              930              935              940

Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945              950              955              960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His
              965              970              975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
              980              985              990

Leu Phe Trp Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln
              995              1000              1005

Leu Ser Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln
1010              1015              1020

Asn Phe Cys Arg Gly Pro Thr Ala Glu
1025              1030

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&lt;211&gt; 1032

&lt;212&gt; PRT

&lt;213&gt; murine

&lt;400&gt; 74

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Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu
          35          40          45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn
50          55          60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn
65          70          75          80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp
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Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met
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Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu
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Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser
130          135          140

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala
145          150          155          160

Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly
          165          170          175

Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro
          180          185          190

Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr
          195          200          205

Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr
210          215          220

Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu
225          230          235          240

Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
          245          250          255

Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser
          260          265          270

Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly
275          280          285

Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe
290          295          300

Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu
305          310          315          320

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Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu  
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 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala  
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 Arg Leu His Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu  
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 370 375 380  
 Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met  
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 405 410 415  
 Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr  
 420 425 430  
 Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu  
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 Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser  
 450 455 460  
 Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu  
 465 470 475 480  
 Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu  
 485 490 495  
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 Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe  
 545 550 555 560  
 Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Thr His Leu Ser  
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 Met Leu Gln Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val  
 580 585 590  
 Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly  
 595 600 605  
 Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe  
 610 615 620  
 Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn  
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 Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu



645 650 655  
 Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr  
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 675 680 685  
 Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu  
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 Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala  
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 885 890 895  
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 Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr  
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 Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser  
 930 935 940  
 Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu  
 945 950 955 960  
 Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His  
 965 970 975  
 Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val

Leu Phe Trp Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln

980                      985                      990  
995                      1000                      1005

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Asn Phe Cys Arg Gly Pro Thr Ala Glu  
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Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu  
35 40 45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn  
50 55 60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn  
65 70 75 80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp  
85 90 95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met  
100 105 110

Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu  
115 120 125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser  
130 135 140

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala  
145 150 155 160

Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly  
165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro  
180 185 190

Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr  
195 200 205

Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr  
210 215 220

Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu  
225 230 235 240

Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg  
 245 250 255  
 Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser  
 260 265 270  
 Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly  
 275 280 285  
 Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe  
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 Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu  
 305 310 315 320  
 Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu  
 325 330 335  
 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala  
 340 345 350  
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 Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu  
 435 440 445  
 Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser  
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 Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu  
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 Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Thr His Leu Ser

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 Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn  
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 965 970 975  
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 35 40 45  
 Ala Thr Thr Thr Leu Asp Leu Ser Tyr Asn Leu Leu Phe Gln Leu Gln  
 50 55 60  
 Ser Ser Asp Phe His Ser Val Ser Lys Leu Arg Val Leu Ile Leu Cys  
 65 70 75 80  
 His Asn Arg Ile Gln Gln Leu Asp Leu Lys Thr Phe Glu Phe Asn Lys  
 85 90 95  
 Glu Leu Arg Tyr Leu Asp Leu Ser Asn Asn Arg Leu Lys Ser Val Thr  
 100 105 110  
 Trp Tyr Leu Leu Ala Gly Leu Arg Tyr Leu Asp Leu Ser Phe Asn Asp  
 115 120 125  
 Phe Asp Thr Met Pro Ile Cys Glu Glu Ala Gly Asn Met Ser His Leu  
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 Glu Ile Leu Gly Leu Ser Gly Ala Lys Ile Gln Lys Ser Asp Phe Gln  
 145 150 155 160  
 Lys Ile Ala His Leu His Leu Asn Thr Val Phe Leu Gly Phe Arg Thr  
 165 170 175  
 Leu Pro His Tyr Glu Glu Gly Ser Leu Pro Ile Leu Asn Thr Thr Lys  
 180 185 190  
 Leu His Ile Val Leu Pro Met Asp Thr Asn Phe Trp Val Leu Leu Arg  
 195 200 205  
 Asp Gly Ile Lys Thr Ser Lys Ile Leu Glu Met Thr Asn Ile Asp Gly  
 210 215 220  
 Lys Ser Gln Phe Val Ser Tyr Glu Met Gln Arg Asn Leu Ser Leu Glu  
 225 230 235 240

Asn Ala Lys Thr Ser Val Leu Leu Leu Asn Lys Val Asp Leu Leu Trp  
 245 250 255  
 Asp Asp Leu Phe Leu Ile Leu Gln Phe Val Trp His Thr Ser Val Glu  
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 His Phe Gln Ile Arg Asn Val Thr Phe Gly Gly Lys Ala Tyr Leu Asp  
 275 280 285  
 His Asn Ser Phe Asp Tyr Ser Asn Thr Val Met Arg Thr Ile Lys Leu  
 290 295 300  
 Glu His Val His Phe Arg Val Phe Tyr Ile Gln Gln Asp Lys Ile Tyr  
 305 310 315 320  
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 325 330 335  
 Gln Met Pro His Met Leu Phe Pro Asn Tyr Pro Thr Lys Phe Gln Tyr  
 340 345 350  
 Leu Asn Phe Ala Asn Asn Ile Leu Thr Asp Glu Leu Phe Lys Arg Thr  
 355 360 365  
 Ile Gln Leu Pro His Leu Lys Thr Leu Ile Leu Asn Gly Asn Lys Leu  
 370 375 380  
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 385 390 395 400  
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 405 410 415  
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 420 425 430  
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 435 440 445  
 Asp Leu Asn Asn Asn Gln Ile Gln Thr Val Pro Lys Glu Thr Ile His  
 450 455 460  
 Leu Met Ala Leu Arg Glu Leu Asn Ile Ala Phe Asn Phe Leu Thr Asp  
 465 470 475 480  
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 485 490 495  
 Met Asn Phe Ile Leu Ser Pro Ser Leu Asp Phe Val Gln Ser Cys Gln  
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 530 535 540  
 Val Gly Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg  
 545 550 555 560  
 Gly Ile Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr



565 570 575  
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 580 585 590  
 Ala Val Ala Phe Cys Cys Leu His Phe Asp Leu Pro Trp Tyr Leu Arg  
 595 600 605  
 Met Leu Gly Gln Cys Thr Gln Thr Trp His Arg Val Arg Lys Thr Thr  
 610 615 620  
 Gln Glu Gln Leu Lys Arg Asn Val Arg Phe His Ala Phe Ile Ser Tyr  
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 Ser Glu His Asp Ser Leu Trp Val Lys Asn Glu Leu Ile Pro Asn Leu  
 645 650 655  
 Glu Lys Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe  
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 Asp Pro Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys  
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 Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu  
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 Cys Ile Pro Thr Arg Tyr His Lys Leu Lys Ala Leu Leu Glu Lys Lys  
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<210> 79

<211> 2753

<212> DNA

<213> Homo sapiens

<400> 79

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<210> 80  
 <211> 796  
 <212> PRT  
 <213> Homo sapiens

<400> 80

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Glu Phe Ala Val Asp Lys Ser Lys Arg Gly Leu Ile His Val Pro Lys
          35          40          45

Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile
          50          55          60

Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val
65          70          75          80

Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe
          85          90          95

Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu
          100          105          110

Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu
          115          120          125

Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn
          130          135          140

Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys
145          150          155          160

Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu
          165          170          175

Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser Leu Gln
          180          185          190

Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr Ser Leu
          195          200          205

Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln
          210          215          220

Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys
225          230          235          240

Phe Leu Ser Glu Leu Thr Arg Gly Pro Thr Leu Leu Asn Phe Thr Leu
          245          250          255

Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe Gln Phe
          260          265          270

Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile
          275          280          285

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Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu  
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 Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser  
 305 310 315 320  
 Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu  
 325 330 335  
 Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro  
 340 345 350  
 Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser  
 355 360 365  
 Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu Ile Leu  
 370 375 380  
 Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys  
 385 390 395 400  
 Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu  
 405 410 415  
 Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val  
 420 425 430  
 Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg Cys Leu  
 435 440 445  
 Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser  
 450 455 460  
 Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val  
 465 470 475 480  
 Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser  
 485 490 495  
 Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro Ser Ala  
 500 505 510  
 Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp  
 515 520 525  
 Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys Asn Ile  
 530 535 540  
 Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys  
 545 550 555 560  
 Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His  
 565 570 575  
 Met Ser Glu Leu Ser Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Gly  
 580 585 590  
 Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr  
 595 600 605  
 Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr Thr

```

        610                615                620
Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu
625                630                635                640

Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val
        645                650                655

Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys
        660                665                670

Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile
        675                680                685

Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro
        690                695                700

Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His
705                710                715                720

His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu
        725                730                735

Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys
        740                745                750

Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser
        755                760                765

Lys Arg Gly Leu Phe Trp Ala Asn Ile Arg Ala Ala Phe Asn Met Lys
        770                775                780

Leu Thr Leu Val Thr Glu Asn Asn Asp Val Lys Ser
785                790                795

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<210> 81
<211> 796
<212> PRT
<213> Homo sapiens

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<400> 81

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Met Thr Lys Asp Lys Glu Pro Ile Val Lys Ser Phe His Phe Val Cys
1                5                10                15

Leu Met Ile Ile Ile Val Gly Thr Arg Ile Gln Phe Ser Asp Gly Asn
        20                25                30

Glu Phe Ala Val Asp Lys Ser Lys Arg Gly Leu Ile His Val Pro Lys
        35                40                45

Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile
        50                55                60

Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val
65                70                75                80

Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe
        85                90                95

Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu
        100                105                110

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Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu  
 115 120 125  
 Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn  
 130 135 140  
 Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys  
 145 150 155 160  
 Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu  
 165 170 175  
 Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser Leu Gln  
 180 185 190  
 Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr Ser Leu  
 195 200 205  
 Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln  
 210 215 220  
 Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys  
 225 230 235 240  
 Phe Leu Ser Glu Leu Thr Arg Gly Ser Thr Leu Leu Asn Phe Thr Leu  
 245 250 255  
 Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe Gln Phe  
 260 265 270  
 Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile  
 275 280 285  
 Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu  
 290 295 300  
 Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser  
 305 310 315 320  
 Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu  
 325 330 335  
 Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro  
 340 345 350  
 Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser  
 355 360 365  
 Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu Ile Leu  
 370 375 380  
 Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys  
 385 390 395 400  
 Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu  
 405 410 415  
 Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val  
 420 425 430  
 Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg Cys Leu



435 440 445  
 Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser  
 450 455 460  
 Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val  
 465 470 475 480  
 Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser  
 485 490 495  
 Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro Ser Ala  
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 Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp  
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 Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys  
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 Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His  
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 580 585 590  
 Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr  
 595 600 605  
 Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr  
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 Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu  
 625 630 635 640  
 Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val  
 645 650 655  
 Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys  
 660 665 670  
 Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile  
 675 680 685  
 Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro  
 690 695 700  
 Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His  
 705 710 715 720  
 His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu  
 725 730 735  
 Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys  
 740 745 750  
 Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser  
 755 760 765  
 Lys Arg Gly Leu Phe Trp Ala Asn Ile Arg Ala Ala Phe Asn Met Lys

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 Leu Thr Leu Val Thr Glu Asn Asn Asp Val Lys Ser  
 785                      790                      795

<210> 82  
 <211> 796  
 <212> PRT  
 <213> Homo sapiens

<400> 82

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                     20                      25                      30  
 Glu Phe Ala Val Asp Lys Ser Lys Arg Gly Leu Ile His Val Pro Lys  
                     35                      40                      45  
 Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile  
                     50                      55                      60  
 Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val  
 65                      70                      75                      80  
 Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe  
                     85                      90                      95  
 Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu  
                     100                      105                      110  
 Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu  
                     115                      120                      125  
 Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn  
                     130                      135                      140  
 Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys  
 145                      150                      155                      160  
 Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu  
                     165                      170                      175  
 Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser Leu Gln  
                     180                      185                      190  
 Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr Ser Leu  
                     195                      200                      205  
 Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln  
                     210                      215                      220  
 Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys  
 225                      230                      235                      240  
 Phe Leu Ser Glu Leu Thr Arg Gly Pro Thr Leu Leu Asn Phe Thr Leu  
                     245                      250                      255  
 Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe Gln Phe  
                     260                      265                      270

Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile  
 275 280 285  
 Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu  
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 Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser  
 305 310 315 320  
 Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu  
 325 330 335  
 Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro  
 340 345 350  
 Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser  
 355 360 365  
 Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu Ile Leu  
 370 375 380  
 Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys  
 385 390 395 400  
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 420 425 430  
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 Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser  
 450 455 460  
 Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val  
 465 470 475 480  
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 485 490 495  
 Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro Ser Ala  
 500 505 510  
 Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp  
 515 520 525  
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 530 535 540  
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 545 550 555 560  
 Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His  
 565 570 575  
 Met Ser Glu Leu Ser Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Gly  
 580 585 590  
 Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr

595                      600                      605  
 Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr  
 610                      615                      620  
 Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu  
 625                      630                      635                      640  
 Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val  
 645                      650                      655  
 Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys  
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 Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser  
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&lt;211&gt; 2421

&lt;212&gt; DNA

&lt;213&gt; murine

&lt;400&gt; 85

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2421

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<400> 86

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Val Gly Ser Met Thr Pro Phe Ser Asn Glu Leu Glu Ser Met Val Asp  
 35 40 45

Tyr Ser Asn Arg Asn Leu Thr His Val Pro Lys Asp Leu Pro Pro Arg  
 50 55 60

Thr Lys Ala Leu Ser Leu Ser Gln Asn Ser Ile Ser Glu Leu Arg Met  
 65 70 75 80

Pro Asp Ile Ser Phe Leu Ser Glu Leu Arg Val Leu Arg Leu Ser His  
 85 90 95

Asn Arg Ile Arg Ser Leu Asp Phe His Val Phe Leu Phe Asn Gln Asp  
 100 105 110

Leu Glu Tyr Leu Asp Val Ser His Asn Arg Leu Gln Asn Ile Ser Cys  
 115 120 125

Cys Pro Met Ala Ser Leu Arg His Leu Asp Leu Ser Phe Asn Asp Phe  
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Asp Val Leu Pro Val Cys Lys Glu Phe Gly Asn Leu Thr Lys Leu Thr  
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Phe Leu Gly Leu Ser Ala Ala Lys Phe Arg Gln Leu Asp Leu Leu Pro  
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Val Ala His Leu His Leu Ser Cys Ile Leu Leu Asp Leu Val Ser His  
 180 185 190

His Ile Lys Gly Gly Glu Thr Glu Ser Leu Gln Ile Pro Asn Thr Thr  
 195 200 205

Val Leu His Leu Val Phe His Pro Asn Ser Leu Phe Ser Val Gln Val  
 210 215 220

Asn Met Ser Val Asn Ala Leu Gly His Leu Gln Leu Ser Asn Ile Lys  
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Leu Asn Asp Glu Asn Cys Gln Arg Leu Met Thr Phe Leu Ser Glu Leu  
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Thr Arg Gly Pro Thr Leu Leu Asn Val Thr Leu Gln His Ile Glu Thr  
 260 265 270

Thr Trp Lys Cys Ser Val Lys Leu Phe Gln Phe Phe Trp Pro Arg Pro  
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 Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile Thr Glu Arg Ile Asp  
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 370 375 380  
 Ser Thr Leu Lys Arg Leu Gln Thr Leu Ile Leu Gln Arg Asn Gly Leu  
 385 390 395 400  
 Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys Asn Met Ser Ser Leu  
 405 410 415  
 Glu Thr Leu Asp Val Ser Leu Asn Ser Leu Asn Ser His Ala Tyr Asp  
 420 425 430  
 Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val Leu Asn Leu Ser Ser  
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 450 455 460  
 Val Leu Asp Leu His Asn Asn Arg Ile Met Ser Ile Pro Lys Asp Val  
 465 470 475 480  
 Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val Ala Ser Asn Ser Leu  
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 Thr Asp Leu Pro Gly Cys Gly Ala Phe Ser Ser Leu Ser Val Leu Val  
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 Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg Cys Asp Tyr Pro Glu  
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 His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe  
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 Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg Ala Leu Met Ala Gln  
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 Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly Lys Arg Gly Leu Phe  
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 Glu Asp Asp Val Lys Thr  
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 <211> 806  
 <212> PRT  
 <213> murine

<400> 87

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 Val Gly Ser Met Thr Pro Phe Ser Asn Glu Leu Glu Ser Met Val Asp  
 35 40 45  
 Tyr Ser Asn Arg Asn Leu Thr His Val Pro Lys Asp Leu Pro Pro Arg  
 50 55 60  
 Thr Lys Ala Leu Ser Leu Ser Gln Asn Ser Ile Ser Glu Leu Arg Met  
 65 70 75 80

Pro Asp Ile Ser Phe Leu Ser Glu Leu Arg Val Leu Arg Leu Ser His  
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                             100                            105                            110  
 Leu Glu Tyr Leu Asp Val Ser His Asn Arg Leu Gln Asn Ile Ser Cys  
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 Cys Pro Met Ala Ser Leu Arg His Leu Asp Leu Ser Phe Asn Asp Phe  
                             130                            135                            140  
 Asp Val Leu Pro Val Cys Lys Glu Phe Gly Asn Leu Thr Lys Leu Thr  
                             145                            150                            155                            160  
 Phe Leu Gly Leu Ser Ala Ala Lys Phe Arg Gln Leu Asp Leu Leu Pro  
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 Val Ala His Leu His Leu Ser Cys Ile Leu Leu Asp Leu Val Ser Tyr  
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 His Ile Lys Gly Gly Glu Thr Glu Ser Leu Gln Ile Pro Asn Thr Thr  
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 Val Leu His Leu Val Phe His Pro Asn Ser Leu Phe Ser Val Gln Val  
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 Asn Met Ser Val Asn Ala Leu Gly His Leu Gln Leu Ser Asn Ile Lys  
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 Thr Trp Lys Cys Ser Val Lys Leu Phe Gln Phe Phe Trp Pro Arg Pro  
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 Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile Thr Glu Arg Ile Asp  
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 Arg Glu Glu Phe Thr Tyr Ser Glu Thr Ala Leu Lys Ser Leu Met Ile  
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 Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys Asn Met Ser Ser Leu

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 Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val Leu Asn Leu Ser Ser  
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 Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val Ala Ser Asn Ser Leu  
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 530 535 540  
 Thr Cys Glu Leu Arg Asp Phe Val Lys Asn Ile Gly Trp Val Ala Arg  
 545 550 555 560  
 Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg Cys Asp Tyr Pro Glu  
 565 570 575  
 Ser Ser Lys Gly Thr Ala Leu Arg Asp Phe His Met Ser Pro Leu Ser  
 580 585 590  
 Cys Asp Thr Val Leu Leu Thr Val Thr Ile Gly Ala Thr Met Leu Val  
 595 600 605  
 Leu Ala Val Thr Gly Ala Phe Leu Cys Leu Tyr Phe Asp Leu Pro Trp  
 610 615 620  
 Tyr Val Arg Met Leu Cys Gln Trp Thr Gln Thr Arg His Arg Ala Arg  
 625 630 635 640  
 His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe  
 645 650 655  
 Val Ser Tyr Ser Glu His Asp Ser Ala Trp Val Lys Asn Glu Leu Leu  
 660 665 670  
 Pro Asn Leu Glu Lys Asp Asp Ile Arg Val Cys Leu His Glu Arg Asn  
 675 680 685  
 Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Asn Phe Ile Glu  
 690 695 700  
 Lys Ser Tyr Lys Ala Ile Phe Val Leu Ser Pro His Phe Ile Gln Ser  
 705 710 715 720  
 Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His  
 725 730 735  
 Glu Gly Ser Asp Asn Leu Ile Leu Ile Leu Leu Glu Pro Ile Leu Gln

740 745 750  
 Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg Ala Leu Met Ala Gln  
 755 760 765  
 Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly Lys Arg Gly Leu Phe  
 770 775 780  
 Trp Ala Asn Leu Arg Ala Ser Phe Ile Met Lys Leu Ala Leu Val Asn  
 785 790 795 800  
 Glu Asp Asp Val Lys Thr  
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<210> 88  
 <211> 806  
 <212> PRT  
 <213> murine

<400> 88

Met Val Lys Ser Leu Trp Asp Ser Leu Cys Asn Met Ser Gln Asp Arg  
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 Val Gly Ser Met Thr Pro Phe Ser Asn Glu Leu Glu Ser Met Val Asp  
 35 40 45  
 Tyr Ser Asn Arg Asn Leu Thr His Val Pro Lys Asp Leu Pro Pro Arg  
 50 55 60  
 Thr Lys Ala Leu Ser Leu Ser Gln Asn Ser Ile Ser Glu Leu Arg Met  
 65 70 75 80  
 Pro Asp Ile Ser Phe Leu Ser Glu Leu Arg Val Leu Arg Leu Ser His  
 85 90 95  
 Asn Arg Ile Arg Ser Leu Asp Phe His Val Phe Leu Phe Asn Gln Asp  
 100 105 110  
 Leu Glu Tyr Leu Asp Val Ser His Asn Arg Leu Gln Asn Ile Ser Cys  
 115 120 125  
 Cys Pro Met Ala Ser Leu Arg His Leu Asp Leu Ser Phe Asn Asp Phe  
 130 135 140  
 Asp Val Leu Pro Val Cys Lys Glu Phe Gly Asn Leu Thr Lys Leu Thr  
 145 150 155 160  
 Phe Leu Gly Leu Ser Ala Ala Lys Phe Arg Gln Leu Asp Leu Leu Pro  
 165 170 175  
 Val Ala His Leu His Leu Ser Cys Ile Leu Leu Asp Leu Val Ser His  
 180 185 190  
 His Ile Lys Gly Gly Glu Thr Glu Ser Leu Gln Ile Pro Asn Thr Thr  
 195 200 205  
 Val Leu His Leu Val Phe His Pro Asn Ser Leu Phe Ser Val Gln Val  
 210 215 220

Asn Met Ser Val Asn Ala Leu Gly His Leu Gln Leu Ser Asn Ile Lys  
 225 230 235 240  
 Leu Asn Asp Glu Asn Cys Gln Arg Leu Met Thr Phe Leu Ser Glu Leu  
 245 250 255  
 Thr Arg Gly Pro Thr Leu Leu Asn Val Thr Leu Gln His Ile Glu Thr  
 260 265 270  
 Thr Trp Lys Cys Ser Val Lys Leu Phe Gln Phe Phe Trp Pro Arg Pro  
 275 280 285  
 Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile Thr Glu Arg Ile Asp  
 290 295 300  
 Arg Glu Glu Phe Thr Tyr Ser Glu Thr Ala Leu Lys Ser Leu Met Ile  
 305 310 315 320  
 Glu His Val Lys Asn Gln Val Phe Leu Phe Ser Lys Glu Ala Leu Tyr  
 325 330 335  
 Ser Val Phe Ala Glu Met Asn Ile Lys Met Leu Ser Ile Ser Asp Thr  
 340 345 350  
 Pro Phe Ile His Met Val Cys Pro Pro Ser Pro Ser Ser Phe Thr Phe  
 355 360 365  
 Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser Val Phe Gln Gly Cys  
 370 375 380  
 Ser Thr Leu Lys Arg Leu Gln Thr Leu Ile Leu Gln Arg Asn Gly Leu  
 385 390 395 400  
 Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys Asn Met Ser Ser Leu  
 405 410 415  
 Glu Thr Leu Asp Val Ser Leu Asn Ser Leu Asn Ser His Ala Tyr Asp  
 420 425 430  
 Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val Leu Asn Leu Ser Ser  
 435 440 445  
 Asn Met Leu Thr Gly Ser Val Phe Arg Cys Leu Pro Pro Lys Val Lys  
 450 455 460  
 Val Leu Asp Leu His Asn Asn Arg Ile Met Ser Ile Pro Lys Asp Val  
 465 470 475 480  
 Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val Ala Ser Asn Ser Leu  
 485 490 495  
 Thr Asp Leu Pro Gly Cys Gly Ala Phe Ser Ser Leu Ser Val Leu Val  
 500 505 510  
 Ile Asp His Asn Ser Val Ser His Pro Ser Glu Asp Phe Phe Gln Ser  
 515 520 525  
 Cys Gln Asn Ile Arg Ser Leu Thr Ala Gly Asn Asn Pro Phe Gln Cys  
 530 535 540  
 Thr Cys Glu Leu Arg Asp Phe Val Lys Asn Ile Gly Trp Val Ala Arg

545                      550                      555                      560  
 Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg Cys Asp Tyr Pro Glu  
                                  565                      570                      575  
  
 Ser Ser Lys Gly Thr Ala Leu Arg Asp Phe His Met Ser Pro Leu Ser  
                                  580                      585                      590  
  
 Cys Asp Thr Val Leu Leu Thr Val Thr Ile Gly Ala Thr Met Leu Val  
                                  595                      600                      605  
  
 Leu Ala Val Thr Gly Ala Phe Leu Cys Leu Tyr Phe Asp Leu Pro Trp  
                                  610                      615                      620  
  
 Tyr Val Arg Met Leu Cys Gln Trp Thr Gln Thr Arg His Arg Ala Arg  
                                  625                      630                      635                      640  
  
 His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe  
                                  645                      650                      655  
  
 Val Ser Tyr Ser Glu His Asp Ser Ala Trp Val Lys Asn Glu Leu Leu  
                                  660                      665                      670  
  
 Pro Asn Leu Glu Lys Asp Asp Ile Arg Val Cys Leu His Glu Arg Asn  
                                  675                      680                      685  
  
 Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Asn Phe Ile Glu  
                                  690                      695                      700  
  
 Lys Ser Tyr Lys Ala Ile Phe Val Leu Ser Pro His Phe Ile Gln Ser  
                                  705                      710                      715                      720  
  
 Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His  
                                  725                      730                      735  
  
 Glu Gly Ser Asp Asn Leu Ile Leu Ile Leu Leu Glu Pro Ile Leu Gln  
                                  740                      745                      750  
  
 Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg Ala Leu Met Ala Gln  
                                  755                      760                      765  
  
 Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly Lys Arg Gly Leu Phe  
                                  770                      775                      780  
  
 Trp Ala Asn Leu Arg Ala Ser Phe Ile Met Lys Leu Ala Leu Val Asn  
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 Glu Asp Asp Val Lys Thr  
                                  805

<210> 89  
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 <212> PRT  
 <213> murine

<400> 89

Met Ser Gln Asp Arg Lys Pro Ile Val Gly Ser Phe His Phe Val Cys  
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                                  20                      25                      30



Glu Ser Met Val Asp Tyr Ser Asn Arg Asn Leu Thr His Val Pro Lys  
 35 40 45  
 Asp Leu Pro Pro Arg Thr Lys Ala Leu Ser Leu Ser Gln Asn Ser Ile  
 50 55 60  
 Ser Glu Leu Arg Met Pro Asp Ile Ser Phe Leu Ser Glu Leu Arg Val  
 65 70 75 80  
 Leu Arg Leu Ser His Asn Arg Ile Arg Ser Leu Asp Phe His Val Phe  
 85 90 95  
 Leu Phe Asn Gln Asp Leu Glu Tyr Leu Asp Val Ser His Asn Arg Leu  
 100 105 110  
 Gln Asn Ile Ser Cys Cys Pro Met Ala Ser Leu Arg His Leu Asp Leu  
 115 120 125  
 Ser Phe Asn Asp Phe Asp Val Leu Pro Val Cys Lys Glu Phe Gly Asn  
 130 135 140  
 Leu Thr Lys Leu Thr Phe Leu Gly Leu Ser Ala Ala Lys Phe Arg Gln  
 145 150 155 160  
 Leu Asp Leu Leu Pro Val Ala His Leu His Leu Ser Cys Ile Leu Leu  
 165 170 175  
 Asp Leu Val Ser Tyr His Ile Lys Gly Gly Glu Thr Glu Ser Leu Gln  
 180 185 190  
 Ile Pro Asn Thr Thr Val Leu His Leu Val Phe His Pro Asn Ser Leu  
 195 200 205  
 Phe Ser Val Gln Val Asn Met Ser Val Asn Ala Leu Gly His Leu Gln  
 210 215 220  
 Leu Ser Asn Ile Lys Leu Asn Asp Glu Asn Cys Gln Arg Leu Met Thr  
 225 230 235 240  
 Phe Leu Ser Glu Leu Thr Arg Gly Pro Thr Leu Leu Asn Val Thr Leu  
 245 250 255  
 Gln His Ile Glu Thr Thr Trp Lys Cys Ser Val Lys Leu Phe Gln Phe  
 260 265 270  
 Phe Trp Pro Arg Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile  
 275 280 285  
 Thr Glu Arg Ile Asp Arg Glu Glu Phe Thr Tyr Ser Glu Thr Ala Leu  
 290 295 300  
 Lys Ser Leu Met Ile Glu His Val Lys Asn Gln Val Phe Leu Phe Ser  
 305 310 315 320  
 Lys Glu Ala Leu Tyr Ser Val Phe Ala Glu Met Asn Ile Lys Met Leu  
 325 330 335  
 Ser Ile Ser Asp Thr Pro Phe Ile His Met Val Cys Pro Pro Ser Pro  
 340 345 350  
 Ser Ser Phe Thr Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser

355 360 365  
 Val Phe Gln Gly Cys Ser Thr Leu Lys Arg Leu Gln Thr Leu Ile Leu  
 370 375 380  
 Gln Arg Asn Gly Leu Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys  
 385 390 395 400  
 Asn Met Ser Ser Leu Glu Thr Leu Asp Val Ser Leu Asn Ser Leu Asn  
 405 410 415  
 Ser His Ala Tyr Asp Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val  
 420 425 430  
 Leu Asn Leu Ser Ser Asn Met Leu Thr Gly Ser Val Phe Arg Cys Leu  
 435 440 445  
 Pro Pro Lys Val Lys Val Leu Asp Leu His Asn Asn Arg Ile Met Ser  
 450 455 460  
 Ile Pro Lys Asp Val Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val  
 465 470 475 480  
 Ala Ser Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ala Phe Ser Ser  
 485 490 495  
 Leu Ser Val Leu Val Ile Asp His Asn Ser Val Ser His Pro Ser Glu  
 500 505 510  
 Asp Phe Phe Gln Ser Cys Gln Asn Ile Arg Ser Leu Thr Ala Gly Asn  
 515 520 525  
 Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Asp Phe Val Lys Asn Ile  
 530 535 540  
 Gly Trp Val Ala Arg Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg  
 545 550 555 560  
 Cys Asp Tyr Pro Glu Ser Ser Lys Gly Thr Ala Leu Arg Asp Phe His  
 565 570 575  
 Met Ser Pro Leu Ser Cys Asp Thr Val Leu Leu Thr Val Thr Ile Gly  
 580 585 590  
 Ala Thr Met Leu Val Leu Ala Val Thr Gly Ala Phe Leu Cys Leu Tyr  
 595 600 605  
 Phe Asp Leu Pro Trp Tyr Val Arg Met Leu Cys Gln Trp Thr Gln Thr  
 610 615 620  
 Arg His Arg Ala Arg His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu  
 625 630 635 640  
 Gln Phe His Ala Phe Val Ser Tyr Ser Glu His Asp Ser Ala Trp Val  
 645 650 655  
 Lys Asn Glu Leu Leu Pro Asn Leu Glu Lys Asp Asp Ile Arg Val Cys  
 660 665 670  
 Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile  
 675 680 685  
 Ile Asn Phe Ile Glu Lys Ser Tyr Lys Ala Ile Phe Val Leu Ser Pro

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      690              695              700
His Phe Ile Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His
705              710              715              720

His Asn Leu Phe His Glu Gly Ser Asp Asn Leu Ile Leu Ile Leu Leu
      725              730              735

Glu Pro Ile Leu Gln Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg
      740              745              750

Ala Leu Met Ala Gln Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly
      755              760              765

Lys Arg Gly Leu Phe Trp Ala Asn Leu Arg Ala Ser Phe Ile Met Lys
      770              775              780

Leu Ala Leu Val Asn Glu Asp Asp Val Lys Thr
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<210> 90
<211> 10
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<220>

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<223> consensus p50 subunit

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<220>
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<223> N = c or t

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<400> 90
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10

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<210> 91
<211> 10
<212> DNA
<213> artificial sequence

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<220>

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<223> consensus p65 subunit

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<223> N = a or g

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<220>
<221> misc_feature
<222> (5)..(5)
<223> N = a, c, g, or t

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<400> 91
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10

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<210> 92

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<220>

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<400> 92  
agttgagggg actttcccag gc

22

<210> 93  
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<212> DNA  
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<220>

<223> CREB binding site

<400> 93  
agagattgcc tgacgtcaga gagctag

27

<210> 94  
<211> 21  
<212> DNA  
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<220>

<223> AP-1 binding site

<400> 94  
cgcttgatga gtcagccgga a

21

<210> 95  
<211> 15  
<212> DNA  
<213> artificial sequence

<220>

<223> AP-1 binding site

<400> 95  
cgcatgagtc agaca

15

<210> 96  
<211> 19  
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<213> artificial sequence

<220>

<223> ISRE

<400> 96

tcgagaagtg aaactgagg 19  
<210> 97  
<211> 11  
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<400> 97  
agaacgaaac a 11  
  
<210> 98  
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<223> ISRE  
  
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gagaagtgaa agtgg 15  
  
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<223> ISRE  
  
<400> 99  
taagaacatg aaactgaa 18  
  
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atgaaactga aagta 15  
  
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<400> 101  
tgaaaaccga aagcgc

16

<210> 102  
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<220>

<223> ISRE

<400> 102  
agaaatggaa agt

13

<210> 103  
<211> 9  
<212> DNA  
<213> artificial sequence

<220>

<223> SRE

<400> 103  
tcaccccac

9

<210> 104  
<211> 10  
<212> DNA  
<213> artificial sequence

<220>

<223> SRE

<400> 104  
ctcaccccac

10

<210> 105  
<211> 10  
<212> DNA  
<213> artificial sequence

<220>

<223> SRE

<400> 105  
gccaccctac

10

<210> 106  
<211> 17  
<212> DNA  
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<220>  
<223> NFAT

<400> 106  
tatgaaacag tttttcc

17

<210> 107  
<211> 9  
<212> DNA  
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<220>

<223> NFAT

<400> 107  
aggaaactc

9

<210> 108  
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<220>

<223> NFAT

<220>  
<221> misc\_feature  
<222> (2)..(2)  
<223> N = a or g

<220>  
<221> misc\_feature  
<222> (5)..(5)  
<223> N = a or g

<400> 108  
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10

<210> 109  
<211> 16  
<212> DNA  
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<220>

<223> NFAT

<400> 109  
ccagttgagc cagaga

16

<210> 110  
<211> 30  
<212> DNA  
<213> artificial sequence

<220>

<223> GAS

<400> 110

ctttcagttt catattactc taaatccatt

30

<210> 111

<211> 10

<212> DNA

<213> artificial sequence

<220>

<223> p53 consensus site

<220>

<221> misc\_feature

<222> (1)..(3)

<223> N = a or g

<220>

<221> misc\_feature

<222> (5)..(6)

<223> N = a or t

<220>

<221> misc\_feature

<222> (8)..(10)

<223> N = c or t

<400> 111

nnncnngnnn

10

<210> 112

<211> 10

<212> DNA

<213> artificial sequence

<220>

<223> p53 consensus site

<400> 112

aggcatgcct

10

<210> 113

<211> 10

<212> DNA

<213> artificial sequence

<220>

<223> p53 consensus site

<400> 113

gggcttgccc

10

<210> 114



<211> 10  
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<400> 114  
gggcttgctt 10  
  
<210> 115  
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<223> p53 consensus site  
  
<400> 115  
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<210> 116  
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<400> 116  
ggacatgccc gggcatgtcc 20  
  
<210> 117  
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<223> p53 consensus site  
  
<400> 117  
gtagcattag cccagacatg tcc 23  
  
<210> 118  
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<212> DNA  
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<220>  
  
<223> TARE  
  
<400> 118  
gaggatgca gacaagagtc agagtttccc cttgaa 36

<210> 119  
<211> 10  
<212> DNA  
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<220>

<223> SRF

<220>  
<221> misc\_feature  
<222> (3)..(8)  
<223> N = a or t

<400> 119  
ccnnnnnnngg

10

<210> 120  
<211> 11  
<212> DNA  
<213> artificial sequence

<220>

<223> SRF

<400> 120  
ccaaataagg c

11

<210> 121  
<211> 670  
<212> DNA  
<213> Homo sapiens

<400> 121  
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aattatattc atattattaa tgtgtatcta tatagatttt tattttgcat atgtactttg 120  
atacaaaatt tacatgaaca aattacacta aaagttattc cacaaatata cttatcaaatt 180  
taagttaaatt gtcaatagct tttaaactta aatttttagtt taacttttct gtcattcttt 240  
actttgaata aaaagagcaa actttgtagt ttttatctgt gaagtagagg tatacgtaat 300  
atacataaat agatatgcca aatctgtgtt attaaaattt catgaagatt tcaattagaa 360  
aaaaatacca taaaaggctt tgagtgcagg tgaaaaatag gcaatgatga aaaaaaatga 420  
aaaacttttt aaacacatgt agagagtgcg taaagaaagc aaaaacagag atagaaagta 480  
caactaggga atttagaaaa tggaaattag tatgttcact atttaagacc tatgcacaga 540  
gcaaagtctt cagaaaacct agaggccgaa gttcaagggt atccatctca agtagcctag 600  
caatatttgc aacatcccaa tggccctgtc cttttcttta ctgatggccg tgctgggtgct 660  
cagctacaaa 670

<210> 122  
<211> 207  
<212> DNA  
<213> Homo sapiens

<400> 122  
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ctttctta at gcttctggac catttccatt tctgtttttg ctttccttct taactcttta 120  
catgagttta gagccgtgtt tctcaaatga tgggctagca cgcgtaagag ctcggtacct 180  
atcgatagag aaatgttctg gcacctg 207

<210> 123  
<211> 161  
<212> DNA  
<213> Homo sapiens

<400> 123  
aggttctctg aaggctttgc ttcttcgaga tgccttaa at agggaaacata ctgatttcca 60  
ctttctta at gcttctggac cactttccat ttctgttttt gctttccttc ttgaactctt 120  
tacatgagtt tagagccgtg tttctcaacc attttgtttt t 161

<210> 124  
<211> 300  
<212> DNA  
<213> Homo sapiens

<400> 124  
ttctcaggtc gtttgctttc ctttgctttc tcccaagtct tgttttacaa tttgctttag 60  
tcattcactg aaactttaaa aaacattaga aaacctcaca gtttgtaaat ctttttcctt 120  
attatatata tcataagata ggagcttaaa taaagagttt tagaaactac taaaatgtaa 180  
atgacatagg aaaactgaaa gggagaagtg aaagtgggaa attcctctga atagagagag 240  
gaccatctca tataaatagg ccatacccac ggagaaagga cattctaact gcaacctttc 300

<210> 125  
<211> 401  
<212> DNA  
<213> Homo sapiens

<400> 125  
gatctgta at gaataagcag gaactttgaa gactcagtga ctgagtgagt aataaagact 60  
cagtgacttc tgatcctgtc ctaactgcc a ctccttggtg tcccaagaaa gcggcttcct 120  
gctctctgag gaggaccctt tccctggaag gtaaaactaa ggatgtcagc agagaaattt 180  
ttccaccatt ggtgcttggt caaagaggaa actgatgagc tcactctaga tgagagagca 240  
gtgagggaga gacagagact cgaatttccg gagctatttc agttttcttt tccgttttgt 300

gcaatttcac ttatgatacc ggccaatgct tggttgctat tttggaaact ccccttaggg 360  
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<210> 126  
<211> 781  
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<213> Homo sapiens

<400> 126  
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tatcatctcc ccaggctctgt gtctgtatga aatgtgcatg ggtgtgtgtg tgcacgcgtg 180  
tgttcccact cggggaatgt ggggagaggt gcatggagcc aagatgggtg gtaaatagta 240  
tgtttctgaa attaaaggac taatgtggag gaaggcgccc cagatgtact aaaccctttg 300  
ccttcatctc atcctctctg acttggaag aaccaggatt ttgtttttaa gcccttgggc 360  
atacagttgt tccatccga catgaactca gcctcccgtc tgaccgccc ttggccttc 420  
ttcttctctg atctgtggaa ccagggaat ctgcctagt ctgtctcaa gcaccttggc 480  
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tcatttcctc ttagttcatt acctgggatt ttgatgtcta tgttccctcc tcgttattga 600  
tacacacaca gagagagaca aacaaaaaag gaacttcttg aaattcccc agaaggtttt 660  
gagagttggt ttcaatgttg caacaagtca gtttctagtt taagtttcca tcagaaagga 720  
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<210> 127  
<211> 277  
<212> DNA  
<213> Homo sapiens

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&lt;400&gt; 130

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&lt;210&gt; 131

&lt;211&gt; 207

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 131

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&lt;210&gt; 132

&lt;211&gt; 645

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 132

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acttagcaaa acctgctggc tgttctctgg gaagtccat gttgcagact cgaaggattt 240  
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aattaggttt cactttccaa aacatgaact gtttcttgaa aaaaagaact tcattgcata 360  
tagaaaaaaa caaagggtgc aatccattct aactataatg ctttttctca acacttaaac 420  
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21